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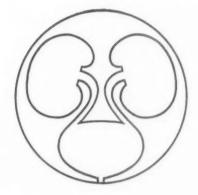
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REFERENCES: 1. Ellis, L. B. et al.: Circulation 17:945, May 1958.
2. Friedlander, H. S.: Am. J. Cardiol. 1:395, Mar. 1958.
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6. Tortora, A. R.: Delaware M. J. 30:298, Oct. 1958.
7. Waldman, S. and Pelner, L.: Am. Pract. & Digest Treat. 8:1075, July 1957.

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The American Journal of Medicine

Vol. XXXI NOVEMBER 1961 No. 5

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Early Recognition and Therapy of Disseminated Coccidioidomycosis

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The problem of early recognition of dissemination of coccidioidomycosis from the localized pulmonary form is of considerable importance in endemic areas, particularly now that effective amphotericin B is available. Based on a large experience, the present authors suggest as criteria for this transition the undue persistence of systemic reactions, the appearance of paratracheal adenopathy in roentgenograms and of physical signs of spread to the sites of predilection, skin test anergy and rise in complement fixation titers, and final confirmation by isolation of the organism from an extrapulmonary site. Early administration of amphotericin B is advised even when dissemination is in doubt.

Cavitary Histoplasmosis Complicated by Fungus Ball JAN SCHWARZ, GERALD L. BAUM AND MANUEL STRAUB 692

"Fungus balls," usually formed by aspergillus, occasionally are found in cavities of the lung, especially bronchiectatic cavities. The balls can be recognized by radiographic examination. Four examples are cited in this report, which includes interesting speculations as to the significance of this phenonemon.

Pulmonary Hyaline Membrane Formation in the Adult. A Clinicopathologic Study Thomas H. Capers 701

Pulmonary hyaline membrane formation is more familiar in infants than in adults, but it does occur and may cause marked dyspnea and death due to respiratory embarrassment. The present analysis makes several points of interest.

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Quality of diabetic control & Quantitation of urine-sugar

In the diagnosis of diabetes, the urine-sugar test may be little more than a screening adjuvant. But in the everyday management of diabetes, the urine-sugar test is the most practical guide we have.' Routine testing, however, should not only detect, but also determine the quantity of urine-sugar. Quantitative testing is essential for satisfactory adjustment of diet, exercise and medication. Furthermore, day-to-day control of diabetes is in the patient's hands. Quality of control is thus best assured by the urine-sugar test which permits the most accurate quantitation practicable by the patient.



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(1) Danowski, T. S.: Diabetes Mellitus, Baltimore, Williams & Wilkins, 1957, p. 239. (2) McCune, W. G.: M. Clin. North America 44:1479, 1960. (3) Ackerman, R. F., et al.: Diabetes 7:398, 1958.

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Left Superior Vena Cava. A Review of Associated Congenital Heart Lesions, Catheterization Data and Roentgenologic Findings

ROBERT S. FRASER, JOSEPH DVORKIN, RICHARD E. ROSSALL
AND RODNEY EIDEM

Of 786 patients studied in reference to heart lesions, in thirty a left superior vena cava was discovered. The significance of this anomaly lies in the difficulties it may cause occasionally in cardiac catheterization; and, because of direct drainage into the left side of the heart, cyanosis may be present. The implications for cardiac surgery are discussed.

Supravalvular Aortic Stenosis. Clinical Experiences with Four Patients Including Familial Occurrence

CHARLES F. WOOLEY, DON M. HOSIER, RICHARD W. BOOTH, WILLIAM MOLNAR, HOWARD D. SIRAK AND JOSEPH M. RYAN

Four additional cases of supravalvular aortic stenosis are added to the growing literature on this anomaly. It should be suspected in the presence of an ejection type murmur and decreased second aortic sound and difference in the blood pressures in the two arms. Its presence may be confirmed by angiocardiography and/or catheterization. Recognition is important since it may not be completely remediable by surgery, since even if obstruction due to the fibrosis band is relieved, coronary artery obstruction may not be helped. Of interest is a familial incidence; two of the cases presented were siblings.

Cardiac Malformation in Mongolism. A Prospective Study of 184 Mongoloid Children
RICHARD D. ROWE AND IRENE A. UCHIDA 726

Now that a characteristic chromosomal anomaly (autosomal trisomy) has been established in mongoloid subjects, the incidence and nature of associated structural defects begins to take on more meaning. In the present fine study of 174 such subjects adequately examined, congenital heart disease was established in seventy (40 per cent). The most common cardiac anomalies were atrioventricularis communis and ventricular septal defect; less frequent were patent ductus arteriosus, atrial septal defect and isolated aberrant subclavian artery. Other correlations are discussed informatively.

Renal Pathology in Paroxysmal Nocturnal Hemoglobinuria. An Electron Microscopic
Illustration of the Formation and Disposition of Ferritin in the Nephron
Martin P. Hutt, James F. Reger and Harry B. Neustein 73

Two cases of paroxysmal nocturnal hemoglobinuria are briefly described. Of interest are the results of scrutiny of kidney tissue from these patients, using electron microscopy as well as light microscopy. By localizing the iron deposits in the various segments of the nephron, in the form of hemosiderin granules, ferritin and siderosomes, it is possible to deduce that hemoglobin is reabsorbed chiefly in the proximal convolution (which accords with stop-flow studies by others) where it is degraded to form hemosiderin and ferritin; these products are then disposed of by transport into the tubular lumen or into the peritubular capillaries.

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more certain control & HYTAKEROL prevention of tetany... HYTAKEROL

rapidly restores the normal calcium-phosphorus ratio.

Indications: Hypoparathyroidism (postoperative and idiopathic), pseudohypoparathyroidism, vitamin D-resistant rickets. Prophylactically, following parathyroid surgery, infant diarrhea that may cause tetany, tetany of pregnancy and premenstrual tetany.

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Immunologic Factors and Resistance to Infection in Chronic Lymphatic Leukemia Daniel G. Miller and David A. Karnofsky 748

While it has long been appreciated that patients with chronic lymphatic leukemia often develop decreased host resistance to infections which makes them unusually vulnerable to a variety of secondary invaders, the precise causes of this phenomenon have not been clearly defined. The present investigators have made an extensive study of the role played by acquired hypogammaglobulinemia, which they find to be present in many patients with chronic lymphatic leukemia. The evidence indicates that failure to generate antibodies adequately is a dominant factor in determining undue susceptibility to infection in these circumstances.

The Relationship of the Latex Fixation Test to the Clinical and Serologic Manifestations of Leprosy

EDGAR S. CATHCART, RALPH C. WILLIAMS, JR., SISTER HILARY ROSS AND EVAN CALKINS

It is well known that non-specific serologic reactions for syphilis and other diseases may be obtained in lepers, so it is perhaps not too surprising that rheumatoid factors, or at least serum proteins giving a positive serologic test for rheumatoid arthritis, also are present. This is well shown in the present study, which revealed a higher proportion of positive reactions with the latex fixation test than with the sheep cell agglutination test—both non-specific. There was no relation between positivity (or titer) of these tests and the duration, type, clinical course or complications of leprosy. The implications are interestingly discussed.

Review

The Latex Fixation Test in Rheumatic Diseases. A Review . . . JACQUES M. SINGER 766

Latex particles have proved useful as inert carriers for serologic reactants not only in the detection of rheumatoid factors, for which the procedure was originally introduced, but also in a variety of other tests. Their use in the latex fixation test for rheumatoid arthritis is here particularly considered in the light of a large investigative and clinical experience with the test. The discussion begins with a brief discussion of what is meant by rheumatoid factors, continues with a consideration of gamma globulin as reactant, latex particle emulsions as lyophobic colloids, the reactions involved in the agglutination of the particles, and ends with an appraisal of the diagnostic usefulness of the test in rheumatoid arthritis.

Clinicopathologic Conference

Abdominal Pain, Hyperpyrexia, Diabetic Ketoacidosis, Oliguria and Convulsions

Clinicopathologic Conference (Washington University School of Medicine).

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Excellent visualization, few or no toxic reactions, minimal movement or discomfort following injection—these are the features of Renografin in cerebral angiography. Similarly impressive results have been produced by Renografin-60 and Renografin-76 in abdominal aortography. Further, Renografin is the medium of choice in pediatric arthrography.

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For full information, see your Squibb Product Reference.

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 An interesting study.
- Serum Lipid Studies in Familial Hypercholesterolemic Xanthomatosis

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The effects of a variety of commonly recommended regimens on the serum lipid levels of a patient with familial hypercholesterolemic xanthomatosis are recorded. Some gave significant falls in serum cholesterol; others were disappointing.

Advertisers' Index on Pages 161 and 162

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1. Lipp, R.G.: Habitual Abortion—Treatment with Parenteral Medroxyprogesterone Acetate, to be published.



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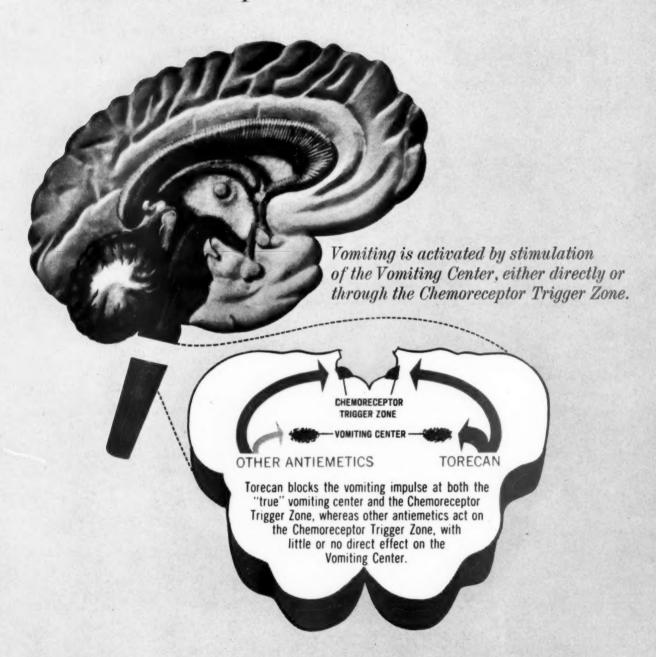
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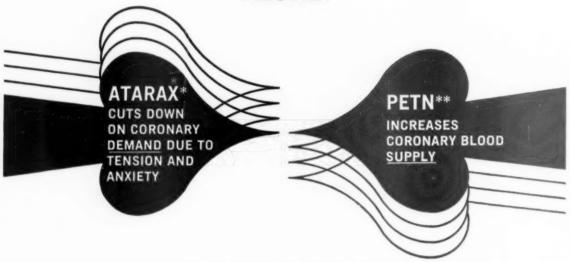
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2-ethyl-mercapto-10-[3'-(1"-methyl-piperazinyl-4")-propyl-1'] phenothiazine dimaleate

HOW

OFFERS
BETTER PROTECTION
AGAINST ANGINA PECTORIS
THAN VASODILATORS
ALONE:



TOGETHER-IN CARTRAX...

they decrease "length, severity, and amount of angina pectoris" in anxious cardiacs.1

Give your angina patient better protection by balancing supply and demand...with CARTRAX.

note: Should be given with caution in glaucoma.

dosage: Begin with 1 to 2 yellow CARTRAX "10" tablets (10 mg. PETN plus 10 mg. Atarax) 3 to 4 times daily. When indicated, this may be increased by switching to pink CARTRAX "20" tablets (20 mg. PETN plus 10 mg. Atarax). For convenience, write "CARTRAX 10" or "CARTRAX 20." Supplied in bottles of 100. Prescription only.

1. Clark, T. E., and Jochem, G. G.: Angiology 11:361 (Aug.) 1960.

*brand of hydroxyzine **pentaerythritol tetranitrate



New York 17, N.Y.
Division, Chas. Pfizer & Co., Inc.
Science for the World's Well-Being*

timed-disintegration

DBI-TI

brand of sustained action phenformin HCI Capsules

blood sugar lowering effects persist for 12 to 14 hours in **stable adult diabetes**

sulfonylurea failures · unstable diabetes



the advantages of phenformin and sustained action are combined in

CAPSULES 50 mg.

...approaches the ideal in oral therapy for stable adult diabetes

each dose lowers blood sugar about 12 to 14 hours

convenient—one dose a day, most, for a great majority of

well tolerated...minimal g.i.

virtually no secondary failures adult diabetes

no liver or other clinical toxic to $2\frac{1}{2}$ years of daily use of DB (nearly 5 years with the DBI tal



od sugar levels for

e a day, or two at ority of patients

imal g.i. side effects

failures in stable

cal toxicity after up se of DBI-TD e DBI tablet)

NOTABLE RECORD OF CLINICAL EFFICACY

in stable adult diabetes up to 88% respond to phenformin.^{1,17} "In our experience the action of DBI on the adult stable type of diabetes is impressive." 1 "There is...a virtual absence of acquired resistance or true secondary failure."

in sulfonylurea failures (primary and secondary) therapy with DBI-TD Capsules³ results in control of a majority of patients.

in labile diabetes DBI-TD Capsules, 5,6,16 as adjunct to injected insulin, often improve regulation of the diabetes.

NOTABLE RECORD OF CLINICAL SAFETY

No clinical toxic effects on the liver, kidney,

or blood due to DBI-TD Capsules or DBI Tablets have been reported 7,8,9,10 following daily use in diabetics for varying periods up to $4\frac{1}{2}$ years. 8 "The absence of hypoglycemic reactions has been conspicuous." 14

DBI-TD Capsules are substantially well tolerated by the gastrointestinal tract^{11,12,13,16,17} when administered as directed.

NOTABLE DOSAGE SIMPLICITY, CONVENIENCE, LOW COST

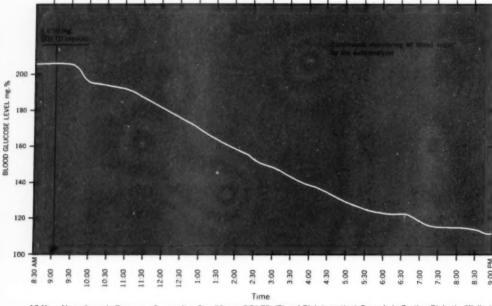
Once-a-day dosage — or at most twice-a-day — makes DBI-TD simple and convenient therapy. Maintenance dosage is readily established and adjustments are infrequently required in the ketosis-resistant patient.

"more convenient, more effective and better tolerated."

DBI-TD—the new convenient and well-tolerated Timed-Disintegration capsule form of DBI—further simplifies effective control of a great majority of diabetics.

Phenformin is believed to exert its hypoglycemic effects primarily by promoting cellular metabolism of glucose via the physiologic Embden-Meyerhof glycolytic pathway.

a single dose of DBI-TD lowers blood sugar for 12 to 14 hours 10,11,12,15



12-Hour Hypoglycemic Response Curve after One 50 mg. DBI-TD (Timed-Disintegration) Capsule in Fasting Diabetic (Weller)

1. Walker, R. S.: Brit. M. J. 2:405, 1959.
2. Hamel, J. F.: Applied Therapeutics 2:137, 1960. 3. Moss, J. M., DeLawter, D. E., Tyroler, S. A., and Field, J. B.: Med. Times 89:561, 1961. 4. Krall, L. P.: Applied Therapeutics 2:137, 1960. 5. Craig, J. W.: Personal communication. 6. White, P. and Krall, L. P.: Personal communication. 7. Miller, E. C., and Roller, G. W.: Med. Times 89:196, 1961. 8. Pomeranze, J.: Clinical Medicine 8:1155, 1961. 9. Barclay, P. L.: J.A.M.A. 174:474, 1960. 10. Krall, L. P.: Med. Clinics N.A. In press. 11. Radding, R. S., and Zimmerman, S. J.: Metabolism 10:238, 1961. 12. Beaser, S. B.: Personal communication. 13. Gurol, F.: Personal communication. 14. Pearlman, W.: Phenformin Symposium, Houston, Feb. 1959. 15. Weller, C., and Linder, M.: Metabolism 10:699, 1961. 16. Fabrycant, M. and Ashe, B. I.: Metabolism 10:684, 1961. 17. Radding, R. S., McHenry, J. I., Neely, W. B., and Lummis, F. R.: Presented at Fourth Congress of Internat. Diabetes Fed., Geneva, June 1961.

DBI-TD (brand of Phenformin HCI-N¹- β -phenethylbiguanide HCI) available as 50 mg. timed-disintegration capsules; bottles of 100 and 1000 capsules. Also available as DBI tablets, 25 mg., bottles of 100 and 1000.

CAPSULES 50 mg.

u. s. vitamin & pharmaceutical corporation

Arlington-Funk Laboratories, division

800 Second Ave., New York 17, N. Y.

administration and dosage: One 50 mg. DBI-TD capsule with breakfast regulates many stable adult diabetics. If higher dosages are needed, a second DBI-TD capsule is added to the evening meal, and further increments (at weekly intervals) to either the A.M. or P.M. dose. In patients requiring insulin, reduction of insulin dosage is made as DBI-TD dosage is increased, until effective regulation is attained. (The acidosisprone, insulin-dependent diabetic should be closely observed for "starvation" ketosis.) Sulfonylurea secondary failures usually respond to relatively low dosages of DBI-TD alone, or combined with reduced dose of sulfonylurea.

side effects: Gastrointestinal reactions occur infrequently and are usually associated with higher dosage levels. They may include unpleasant, metallic taste in the mouth. continuing to anorexia, nausea, and, less frequently, vomiting and diarrhea. They abate promptly upon reduction of dosage or temporary withdrawal. In case of vomiting, DBI-TD should be withdrawn immediately.

precautions: Particularly during the initial period of dosage adjustment, every precaution should be observed to avoid acidosis and coma or hypoglycemic reactions. Hypoglycemic reaction has been observed on rare occasions in the patient treated with insulin or a sulfonylurea in combination with DBI-TD. "Starvation" ketosis, that is the appearance of acetonuria in the presence of a lowered or normal blood sugar. must be distinguished from "insulin-lack" ketosis which is accompanied by hyperglycemia and acidosis. A reduction in the dose of DBI-TD of 50 mg. per day (with a slight increase in insulin as required), and/or a liberalization in carbohydrate intake rapidly restores metabolic balance and eliminates the "starvation" ketosis. Do not increase DBI-TD dosage or give insulin without first checking blood and urine sugars.

caution and contraindication:
As with any oral hypoglycemic therapy reasonable caution should be observed in severe preexisting liver disease. The use of DBI-TD alone is not recommended in the acute complications of diabetes: acidosis, coma, infections, gangrene or surgery.

Complete detailed literature is available to physicians.

Every illness includes some nutritional, metabolic disturbance either directly or indirectly.

Keep informed of new developments in:

Nutrition

Metabolism

Endocrinology

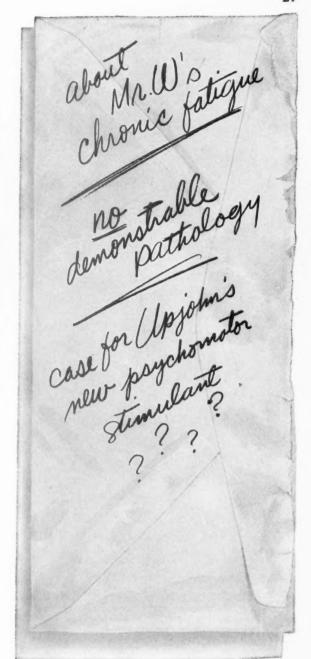
Diet Therapy

Read——
The American Journal
of Clinical Nutrition
(now a monthly)

WRITE FOR YOUR FREE SAMPLE COPY

The American Journal of Clinical Nutrition

466 LEXINGTON AVENUE NEW YORK 17, N.Y.



FOR COMPLETE DETAILS ON



SEE PAGE 42-43

Upjohn

75th year

REMESSE. POLYTHIAZIDE

a more clinically useful diuretic/antihypertensive

IN BRIEF

RENESE (polythiazide) is a new, highly potent, orally effective, nonmercurial diuretic, saluretic, and antihypertensive agent with a high therapeutic index, low order of toxicity, and an intrinsically prolonged duration of action which enhances the excretion of sodium and chloride by the renal tubules.

INDICATIONS: RENESE is indicated for the treatment of hypertension and edema. It has been found useful in congestive heart failure, fluid retention of pregnancy, premenstrual tension, obesity (where fluid retention is present), renal edema, cirrhosis, drug-induced edema, and toxemia of pregnancy.

ADMINISTRATION AND DOSAGE: Initial dose: Depending on the severity of the conditions, initial doses of RENESE may range from 1 mg. to 4 mg. daily (refractory cases may require as much as 12 mg. daily). Maintenance dose: Usual effective maintenance doses range from 1 mg. to 4 mg. daily, depending on the severity of the cases. Some patients have responded to 1 mg. every other day (0.5 mg. daily).

SIDE EFFECTS AND PRECAUTIONS: Since all diuretic agents may reduce serum levels of sodium, chloride, and po-

tassium, patients on RENESE should be observed regularly for early signs of fluid or electrolyte imbalance. Caution must be exercised during digitalis administration to prevent hypokalemia since patients are then more sensitive to the development of digitalis toxicity. During RENESE therapy of edema in patients with chronic renal disease, routine precautions should be taken against renal failure as indicated by an increasing blood urea nitrogen. Like other thiazide diuretics, RENESE may cause a rise in serum uric acid levels and should therefore be used with caution in patients with gout. Should overt manifestations of gout appear, the concomitant use of uricosuric agents may be effective in relieving the symptoms. Side effects with RENESE, such as nausea, vertigo, weakness, and fatigue are infrequent and seldom require cessation of therapy. Most of these reactions may be overcome by reducing the dose of RENESE or by taking measures to improve any electrolyte imbalance. Mild maculopapular skin rash has been rarely reported. Extra precautions may be necessary in patients who may require norepinephrine, or curare or its derivatives.

SUPPLIED: RENESE is available as 1 mg., white, scored tablets in bottles of 30; 2 mg., yellow, scored tablets in bottles of 30; 4 mg., white, scored tablets in bottles of 30.

More detailed professional information available on request.



A MORE CLINICALLY USEFUL DIURETIC/ANTIHYPERTENSIVE

active antihypertensive broad benefit clinically confirmed convenient control dosage dexterity dependable diuresis enhanced effectiveness foremost flexibility increased individualization long lasting

marked micturition notable natruresis orally optimal peak potency prolonged performance reliable response significant saluresis tested toleration unsurpassed utility valuable versatility

"foremost flexibility" - The clinical effectiveness and favorable sodium/potassium ratio of RENESE at 0.5 mg. and at 16 times that dose (8 mg.) may make thiazide therapy available to patients previously excluded either by intolerance at the lowest available doses of other agents or by lack of response at their highest effective doses. The availability of RENESE in 1 mg., 2 mg., and 4 mg. scored tablets provides a dosage form for each and every patient - mild, moderate or severe.

considerably less tense



BUTISOL SODIUM

"was found to be the most effective sedative which will produce satisfactory daytime sedation...with minimal occurrence of untoward reactions."

· Reen-eyed and alert BUTSOL sodium.

butabarbital sodium

In a five-year study² of representative sedative and attractic agents, BUTISOL SODIUM provided the highest therapeutic index (per cent of effectiveness: per cent of untoward reactions) for control of anxiety and insomnia by daytime dosage. "The therapeutic index as defined in this study reflects clinical usefulness and indicates to what degree a sedative agent approaches the ideal." It is significant that phenobarbital, although widely used in anxiety states, falls far short of the ideal.

BUTISOL SODIUM® Tablets Repeat-Action Tablets Elixir/Capsules



McNEIL LABORATORIES, INC., Fort Washington, Pa.

1. Grossman, A. J., Batterman, R. C., and Leifer, P.: Comparative Testing of Daytime Sedatives and Hypnotic Medications, Fed. Proc. 17:373 (March) 1958.

2. Batterman, R. C., Grossman, A. J., Leifer, P., and Mouratoff, G. J.: Clinical Re-evaluation of Daytime Sedatives, Postgrad. Med. 26:502-509 (October) 1959. Now! 2 appetizing foods make serum cholesterol control easier, more effective than ever!



For good eating while maintaining serum cholesterol control

Leading authorities agree that where reduction of serum cholesterol levels is indicated, fat intake should not exceed ½ of total calories and of this, at least ½ should be polyunsaturated fats.

Polyunsaturated fats, such as those found in corn oil, are rich in the linoleates which are important in reducing serum cholesterol levels. This has been proven time and again in nutritional studies of hypercholesterolemia. Mazola Margarine and Mazola Corn Oil have outstanding P/S (polyunsaturate to saturate) ratios. Thus the hypercholesterolemic patient can usually enjoy the same appetizing foods as the rest of the family.

Mazola Corn Oil is unexcelled in polyunsatu-

rates and lowest in saturates of all leading brands of vegetable oils. Mazola's P/S ratio is far higher than that of any other leading food oil. Your patient will find Mazola Corn Oil ideally suited for salad dressings and frying; also for baking wherever liquid shortenings are called for in the recipe.

Mazola Margarine contains liquid Mazola Corn Oil as a major ingredient. This corn oil is not hydrogenated, thereby preserving its rich content of linoleates. Mazola Margarine contains 2 to 3 times as much natural linoleates as any other margarine readily available in grocery stores from coast to coast. Its taste, color and handling characteristics are unexcelled.

AVERAGE COMPOSITIONS OF MAZOLA® MARGARINE AND MAZOLA® CORN OIL

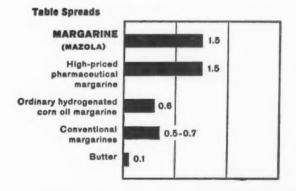
(All figures are in grams.)

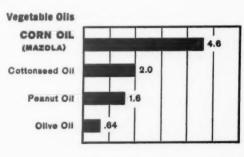
	MAZOLA	MARGARINE	MAZOLA CORN OIL		
F-11-1-1-1	100 grams	2 oz. (4 tbsp.)	100 grams	1 fl. oz. (2 tbsp.)	
Fatty Acids Polyunsaturated	21	12	51	14	
Monounsaturated	40	23	32	9	
Saturated	14	8	11	3	
Natural Sitosterols	0.5	0.3	1	0.3	
Natural Tocopherols	0.08	0.045	0.08	0.020	
Cholesterol	none	none	none	none	
Sodium	0.9	0.5	none	none	

MAZOLA MARGARINE -410 Calories/2 oz.; lodine Value -96
MAZOLA CORN OIL -250 Calories/fi. oz.; lodine Value -124

RATIO OF POLYUNSATURATES/SATURATES

(Average values.)





Write for a copy of A MEAL PATTERN FOR THE HYPERCHOLESTEROLEMIC PATIENT. Contains 25 individual instruction sheets for your patients.

CORN PRODUCTS COMPANY 10 East 56th Street, New York 22, N.Y.



Low-back patient and muscle back in action

Prompt relief...early recovery—In low-back cases, or for any patient with inflammatory or traumatic musculoskeletal complaints, Rela offers prompt relief and the assurance of early recovery. In a study¹ of 212 conservatively treated low-back patients, 106 treated also with carisoprodol [Rela] were 'back in action' in one-fourth the time it took the conventionally treated group. Rela speeds recovery by a combination of effects—analgesic

and muscle relaxant—to reduce spasm and tension, relieve pain, restore mobility. Undesirable effects have been minimal.

SUPPLIED: Bottles of 30, 350 mg. tablets. REFERENCE: 1. Kestler, O. C.: J. A.M. A. 172:2039 (April 30) 1960. For complete details, consult latest Schering literature available from your Schering Representative or the Medical Services Dept., Schering Corporation, Bloomfield, New Jersey. 11-401

RELA

Schering

YPERTENSION

more often than any other diuretic

"Since the chlorothiazide compares well in effectiveness with other hypotensive drugs, it is our practice to initiate therapy with chlorothiazide alone in all patients with normal renal function. In the absence of signs indicating urgency in the reduction of pressure we find it advisable to continue such treatment for one or two months."

Conway, J., and Lauwers, P.: Circulation 21:21, January, 1960.

Supplied: 250-mg. and 500-mg. scored tablets DIURIL chlorothiazide in bottles of 100 and 1000.

Before prescribing or administering DIURIL, the physician should consult the detailed information on use accompanying the package or available on request. DIURIL is a trademark of Merck & Co., INC.



MERCK SHARP & DOHME Division of Merck & Co., INC.

West Point, Pa.

EFFECTIVE MANAGEMENT OF HYPERTENSION BEGINS



WITH DIURIL



when <u>anxiety and tension</u> aggravate pain

EQUANIL® (Meprobamate, Wyeth) and ZACTIRIN® (Ethoheptazine Citrate with Acetylsalicylic Acid, Wyeth)

Relieves pain, relaxes mind and muscle

- analgesic action to relieve pain
- calming action to relieve anxiety
- muscle-relaxant action to relieve spasm and tension

EQUAGESIC RELIEVES PAIN AND ANXIETY

For your patients suffering pain accompanied by anxiety and tension, Equagesic provides gratifying relief. Potent, non-narcotic analgesia is provided by a combination of the potent analgesic, ethoheptazine citrate, with time-proved aspirin. The muscle-relaxant and anti-anxiety effects of meprobamate, coupled with the analgesic agents provide analgesia in depth.

These effective agents relieve the painful anxiety and tension of patients suffering from strains, sprains, muscle tension and other musculo-skeletal conditions. The comforting pain relief afforded by Equagesic is rarely hampered by side effects.^{1,2}

Satisfactory Pain Relief in 97% of patients with painful musculoskeletal conditions. In a study¹ of 106 patients suffering musculoskeletal pain associated with anxiety and muscle spasm, EQUAGESIC "... was extraordinarily effective, satisfactory results being obtained in 97% of the patients treated." EQUAGESIC provided effective pain relief for these conditions:

osteoarthritis • bursitis • low back syndrome tenosynovitis • whiplash injuries • fractures of small bones • tension headache

Gratifying Pain Relief in 74% of patients with painful ligament sprains. In a study² of 104 ambulatory cases of acute cervical or lumbar muscle ligament sprain treated with EQUAGESIC, "... control of acute pain was obtained in 74% of the cases." The conditions treated occurred in typical office patients with pain following injuries to the cervical and/or lumbar spine. The author concluded "... EQUAGESIC (Wyeth) is a satisfactory and useful additional tool in the care of the acute injuries due to muscle ligament sprain..."

1. Splitter, S.R.: Current Therapeutic Research 2:169 (June) 1960. 2. Harsha, W.N.: J. Okla. State Med. Assoc. 54:12 (Jan.) 1961.

For further information on limitations, administration and prescribing of Equagesic, see descriptive literature or current Direction Circular.

Wyeth Laboratories • Philadelphia 1, Pa.

still available!
a limited number of copies of
The Symposium

on

Diagnostic Enzymology

Price \$4.00

This appeared in the December 1959 Issue of

The American Journal of Medicine
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NEW YORK 17, N.Y.



Can we measure the patient's comfort?

Not objectively, as the BMR can be measured by vital capacity tests.

The higher level of relief reported with this new corticosteroid is a subjective thing that must be seen, by you, in your own patients.

Alphadrol*

Upjohn
75th year

See page 127 for description, indications, dosage, precautions, side effects, and how supplied.

The Upjohn Company, Kalamazoo, Michigan copyright 1961, The Upjohn Company August, 1961

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Helps you take the misery out of menopause

as hormones alone often don't do



Fast-acting Milprem directly relieves both emotional dread and estrogen deficiency

Dosage: One Milprem tablet t.i.d. in 21-day courses with one-week rest periods; during the rest periods, Miltown alone can sustain the patient.

Composition: Miltown (meprobamate) + conjugated estrogens (equine).

Supplied: Milprem-400, each coated pink tablet contains 400 mg. Miltown and 0.4 mg. conjugated estrogens (equine). Milprem-200, each coated old-rose tablet contains 200 mg. Miltown and 0.4 mg. conjugated estrogens (equine). Both potencies in bottles of 60.

Literature and samples on request.

Many physicians find that estrogen therapy is not enough for the woman who is also filled with anxiety by her menopause. Her emotional dread may make her so miserable that it becomes a real clinical problem.

This is where Milprem helps you so much. It calms the woman's anxiety and tension; prevents moody ups and downs; relieves her insomnia and headache. At the same time, it checks hot flushes by replacing lost estrogens. The patient feels better than she did on estrogen therapy alone. And your counsel and your assurances can now help her make her adjustment much faster.

(Miltown® plus natural estrogens)

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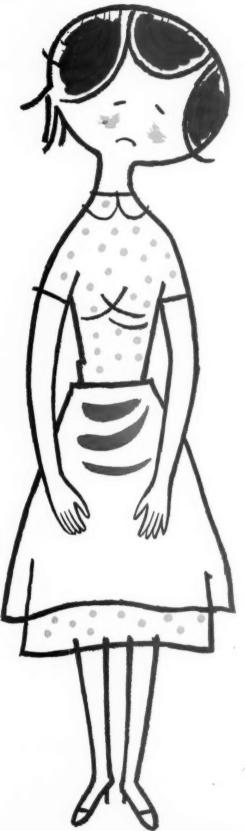


WALLACE LABORATORIES/Cranbury, N. J.

IRON: often a minus

in moms and minors...







LIVITAMIN

... the hematinic with built-in nutritional support

Many growing children and most women of menstrual age deplete their iron reserves and slide into iron-deficiency anemia.

Livitamin changes the minus to a plus because it restores depleted iron reserves and also provides integrated nutritional support.

Iron in Livitamin is well absorbed, with minimum gastric upset and constipation. And with Livitamin there is no worry about teeth stain... or taste acceptance.

WRITE FOR LITERATURE
AND DOSAGE INFORMATION.

FORMULA: Each fluidounce contains:

Iron, peptonized	. 420 mg.
Manganese citrate, soluble, N.F	. 158 mg.
Thiamine hydrochloride	. 10 mg.
Riboflavin	10 mg.
Cobalamin	. 20 mcg.
Nicotinamide	50 mg.
Pyridoxine hydrochloride	. 1 mg.
Pantothenic acid	5 mg.
Liver fraction 1	1 Gm.
Rice bran extract, U.S.P. XIV	1 Gm.
Inositol	. 30 mg.
Choline	60 mg.

SUPPLIED: Liquid: 8 oz. bottles, pints, gallons; Copules: Bottles of 100, 500, 1000. Also available as LIVITAMIN with INTRINSIC FACTOR: bottles of 100 capsules.

THE S. E. MASSENGILL COMPANY

Bristol, Tennessee

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a quiet little revolution

INFLAMMATORY NEURITIS used to take three to six weeks for recovery. However, life was seldom threatened, recovery was all but certain and no headlines were made when published studies indicated that Protamide could usually reduce these weeks to as many days.

Nevertheless a quiet revolution has taken place in this small province of medicine. Protamide is not indicated in mechanical nerve trauma. But when the nerve root is inflamed as, typically, after a virus infection or in herpes zoster, Protamide may be considered as the treatment of choice.¹⁻⁴

START PROTAMIDE EARLY—When treatment is begun within a week after onset of symptoms, two or three injections of Protamide bring not only relief from pain but prompt recovery in almost all patients. In cases not seen early, therapy must of necessity be longer.

PROTAMIDE®—an exclusive colloidal solution of processed and denatured enzyme—is *not* foreign protein therapy.

Boxes of 10 ampuls, 1.3 cc. each, for intramuscular injection.

FOR DETAILED INFORMATION WRITE MEDICAL DEPARTMENT OF

Sherman Laboratories

DETROIT 11, MICHIGAN

Baker, A. G.: Penn. Med. J. 63:697 (May) 1960. 2. Sforzolini, G. S.: Arch. Ophthal. 62:381 (Sept.) 1959. 3. Smith R. T.: Med. Clin. N. Amer. (Mar.) 1957. 4. Lehrer, H. W.; Lehrer, H. G., and Lehrer, D. R.: Northw. Med. (Nov.) 1955.

FOR COUGH AND COLD DEMONS



The ULO family in the management

NON-NARCOTIC

chlophedianol hydrochloride

SYRUP

A single chemical entity, alpha-(2-dimethylaminoethyl)o-chlorobenzhydrol hydrochloride, generically termed chlophedianol hydrochloride.

for control of acute cough regardless of etiology

cough suppressant action

equal nai

narcotics

duration of action

greater

narcotics

The cough suppressant power of ULO is fully as great as that of the narcotics though it reaches peak action somewhat more slowly.

After reaching peak action, ULO maintains its maximal cough-suppressant effect undiminished for 4 to 8 hours.

side action less

narcotics

ULO is free from the limitations and undesirable side effects of narcotics ... no constipation; no gastric irritation; no appetite suppression; no tolerance development; no respiratory depression.

of coughs and colds

ULOMINIC

SYRUP

for control of acute cough & associated allergic reactions

INHIBITS COUGH IMPULSE FOR 4-8 HOURS

the threshold of the medullary cough center is elevated while the cough reflex is not abolished

COUNTERACTS IRRITATION IN PHARYNX, LARYNX, TRACHEA AND BRONCHI

inhibits tendency of histamine to cause edema of the nasopharyngeal mucosa, local irritation, and vasodilation

RELIEVES CONGESTION

reduces postnasal discharge, lessens irritation to pharyngeal and laryngeal membranes

MAKES VOLUNTARY COUGH MORE PRODUCTIVE

loosens and liquefies mucus, soothes irritated bronchial mucosa

ULO®

non-narcotic antitussive molecule chlophedianol HCI

DIAFEN®

fast-acting antihistaminic diphenylpyraline HCI

PHENYLEPHRINE HCI

sympathomimetic

GLYCERYL GUAIACOLATE

expectorant and demulcent

ULOGESIC

TABLETS

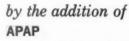
for control of acute cough and relief from associated muscular aches, pain & fever

ULOGESIC ENLARGES THE THERAPEUTIC DIMENSIONS OF ULOMINIC

Ulogesic also

ALLEVIATES ASSOCIATED ACHES AND DISCOMFORTS AND ABORTS FEVER

elevates the pain threshold with an analgesic potency the same as acetanilid, with much less toxicity

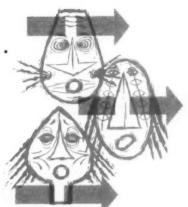


acetyl-p-aminophenol analgesic and antipyretic

FOR CONTROL OF ACUTE COUGH AND COLD

ULO ULOMINIC

DEMONS...



INDICATIONS:

For acute cough associated with:

Upper Respiratory Infections Bronchitis Common Cold **Tracheitis** Influenza Laryngitis Pneumonia Croup Pertussis Pleurisy

Coughs Associated with Allergy (Ulominic and Ulogesic)

Although no contraindications for ULOMINIC or ULOGESIC are known, they

should be used only for acute cough.

Since ULOMINIC and ULOGESIC contain an antihistaminic agent, drowsiness may occur. As they also contain a sympathomimetic agent, they should be used with caution in coronary artery disease, glaucoma, hypertension, and hyperthyroidism.

These occur only occasionally and have been mild. Nausea and dizziness have occurred infrequently; vomiting and drowsiness rarely. As with all centrally acting drugs, an infrequent case may develop excitation, hyperirritability and nightmares. The symptoms disappear within a few hours after the drug is discontinued. In three cases (1 adult and 2 children) where the drug was continued in large or even excessive amounts after stimulation was present, hallucinations developed. Upon withdrawal of the medication, the patients recovered rapidly within a few hours.

Side effects from ULOMINIC or ULOGESIC occur occasionally and are mild. Nausea, dizziness, and dryness of the mouth occur infrequently; vomiting and drowsiness rarely.

Adults: 25 mg. (1 teaspoonful) 3 or 4 times daily as required. Children: 6 to 12 years of age-12.5 to 25 mg. (1/2 to 1 teaspoonful) 3 or 4 times daily as required;

2 to 6 years of age-12.5 mg. (1/2 teaspoonful) 3 or 4 times daily as required.

HILOGESIC

Adults: One teaspoonful (5 cc) four times daily. Children: 6 to 12 years - 1/2 teaspoonful (2.5 cc) 4 times daily. 2 to 6 years-1/4 teaspoonful (25 drops) 4 times daily.

Adults: Two tablets 4 times daily. Children: 6 to 12 years - one tablet 4 times daily.

ULO SYRUP: Bottles 12 oz.

ULOMINIC SYRUP: Bottles 1 pint.

ULOGESIC Riker, Bottles of 100 tablets.

CONTRAINDICATIONS:

CAUTION:

SIDE EFFECTS:

DOSAGE:

AVAILABILITY:

FORMULAS

Each 5 ml. teaspoonful contains: alpha-(2-dimethylamino ethyl)-ochlorobenzhydrol HCl 25 mg. chloroform, U.S.P..... 0.001 ml.

Alcohol 6.65 per cent in a pleasant flavored syrup base

ULOMINIC Each teaspoonful (5 cc) contains: chlophedianol HCI* (alpha-(2-dimethylaminoethyl)-o-chlorobenzhydrol-HCl) . . 15.0 mg. diphenylpyraline HCI (1-methyl-4-piperidyl-benzhydryl ether·HCl) 1.0 mg. 5.0 mg. glyceryl guaiacolate......100.0 mg. alcohol...... 6.0%

Each tablet contains: chlophedianol HCI* (alpha-(2-dimethylaminoethyl)-o-chlorobenzhydrol·HCl) . . 7.5 mg. diphenylpyraline HCI (1methyl-4-piperidyl-benzhydryl 0.5 mg. 2.5 mg. phenylephrine HCI.....

glyceryl guaiacolate...... 25.0 mg.

acetaminophen......162.5 mg.

*Patents pending

CAUTION: Federal law prohibits dispensing without prescription



LABORATORIES, INC. Northridge, California

Hypertension and congestive failure controlled with Serpasil'- Esidrix'



Mr. H.V., a 61-year-old retired pharmacist with hypertensive arteriosclerotic heart disease, was hospitalized in 1957 after a myocardial infarction. Blood pressure at this time ranged from 176/100 to 184/106 mm. Hg. The patient had associated congestive failure with ankle edema and dyspnea.

Serpasil-Esidrix Tablets #1 were added to the existing regimen of digitalis and low-salt diet in April, 1959. In the first 6 weeks of treatment, blood pressure decreased steadily to a range of 156/80 to 166/84 mm. Hg. Examination at the end of 6 weeks revealed no evidence of congestive failure. Neck veins were no longer distended; ankle edema was not present.

Mr. V.'s blood pressure is now stabilized at a satisfactory level and he has had no side effects from Serpasil-Esidrix. He can climb stairs without shortness of breath; he gets around more easily and feels better generally.



Serpasil-Esidrix combines in one tablet the antihypertensive and calming effects of Serpasil with the diuretic and anti-hypertensive-potentiating actions of Esidrix—for control of high blood pressure plus many complications.

SUPPLIED: Tablets #2 (light orange), each containing 0.1 mg. Serpasil and 50 mg. Esidrix; bottles of 100. Tablets #1 (light orange), each containing 0.1 mg. Serpasil and 25 mg. Esidrix; bottles of 100.

SERPASIL® (reserpine CIBA)
ESIDRIX® (hydrochlorothiazide CIBA) For complete information about Serpasil-Esidrix (including dosage, cautions, and side effects), see 1961 Physicians' Desk Reference or write CIBA, Summit, N.J.

Serpasil'- Esidrix'

(reserpine and hydrochlorothiazide cisa)



"If of thy mortal goods thou art bereft,

And from thy slender store two loaves alone to thee are left,

Sell one, and with the dole

Buy hyacinths to feed thy soul."

-Muslih-ud-Din Saadi

Upjohn

75th year

Man does not live by bread alone.

If he did, medicine would be purely a science, concerned only with "bread to nourish the body."

Thoughtful physicians have long recognized the equal essentiality of "hyacinths to feed the soul." This is the art of medicine.

If yours is a typical practice, many of the patients who come to you have no demonstrable somatic pathology. Yet their symptoms often are myriad: low back pain, recurrent headaches, insomnia, anorexia, chronic fatigue, apathy, inability to concentrate, "blues."

While tranquilizers may be indicated in some of these patients, many of them are candidates for the simple psychomotor stimulating effect of Monase. Tests in more than 4,000 patients justify the expectation that Monase will enable many of these patients to sleep better, eat better, and feel better.

For the 4 out of 10 patients with no demonstrable pathology, consider



*TRADEMARK, REG. U.S. PAT. OFF. †ESTIMATED AVERAGE IN GENERAL PRACTICE COPYRIGHT, 1961, THE UPJOHN COMPANY

Description: Monase is etryptamine acetate, a unique non-hydrazine compound, developed in the Upjohn Research Laboratories.

Indications: Various depression states: manic-depressive reaction, depressed type; involutional psychotic reactions with depressed features; psychotic depressed reactions; psychoneurotic depressive reactions; psychiatric disorders with prominent de-pressive symptoms or features; transient situational personality disorders with path-ological depressive features.

Dosage: 30 mg, daily in divided doses, Initial Dosage: 30 mg. daily in divided doses. Initial benefit may be observed within 2-3 days, but maximum results may not be apparent until after 2 or more weeks. Adjustment of dose to individual response should be effected in increments or decrements of 15 mg. daily at weekly intervals. The daily maintenance dose ranges between 15 and 45 mg. In schizophrenics, 30 mg. daily may be useful as an adjunct in activating these patients or brightening their mood. brightening their mood.

Contraindications and Precautions: There are no known absolute contraindications to Monase therapy. However, the drug should be used with caution in schizoid or schizophrenic patients, paranoids, and in patients with intense anxiety, as it may contribute to the activation of a latent or incipient psychotic process. Patients with suicidal tendencies should be kept under careful observation during Monase therapy until such time as the self-destructive tendencies are brought under control.

Patients who are on concomitant antihypertensive therapy should be watched carefully for possible potentiation of hypotensive ef-fects. Added caution should be employed in patients with cardiovascular disease in view

patients with cardiovascular disease in view of the occasional occurrence of postural hypotension, and the possibility of increased activity as a result of a feeling of increased well being.
Despite the fact that liver damage or blood dyscrasias have not been reported in patients receiving Monase, as is the case with any new drug, patients should be carefully observed for the development of these complications. Monase should probably not be used in patients with a history of liver disease. used in patients with a history of liver disease or abnormal liver function tests. Also the usual precautions should be employed in patients with impaired renal function, since it is possible that cumulative effects may occur in such patients.

occur in such patients.

Monase should be employed with caution in patients with epilepsy since the possibility exists that the epileptic state may be aggravated. Also because of its autonomic effects, therapy with Monase may aggravate glaucoma or may produce urinary retention. Monase must not be administered concominantly with impression. tantly with imipramine. In patients receiving Monase caution should be employed in administering the following agents or related compounds in view of possible lowering of the margin of safety: meperidine, local anesthetics (procaine, cocaine, etc.), phenylephrine, amphetamine, alcohol, ether, bar-biturates or histamine.

Toxicity and Side Effects: The side effects observed in patients on Monase therapy in general have been mild and easily managed by symptomatic therapy or dose reduction. If such side effects persist of are severe, the drug should be discontinued. Alterations in blood pressure, usually in the form of postural hypotension, or more rarely, an eleva-tion of blood pressure have been reported. Other side effects include allergic skin reactions and drug fever and those that appear to be dose related since they are more likely to occur when the daily dose exceeds 60 mg. These are nausea and gastrointestinal upset, headache, vertigo, palpitation, dryness of the mouth, blurred vision, over-stimulation of the central nervous system, restlessness, insomnia, paradoxical somnolence and fatigue, muscle weakness, edema, and sweating. Following sudden withdrawal of medication in patients receiving high doses for a prolonged period. There may occur a "rebound" withdrawal effect which is characterized by headache, central nervous s tem hyperstimulation and occasionally hallucinations.

Supplied: 15 mg. compressed tablets in bottles of 100 and 500.

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IN BRIEF

ATARAXOID contains the glucocorticoid prednisolone and the ataractic agent, hydroxyzine.

ADVANTAGES: ATARAXOID combines the tension-relieving effects of hydroxyzine with the anti-inflammatory action of prednisolone, a well-established corticosteroid, for superior control of the signs and symptoms of rheumatoid arthritis without unexpected side effects. An important result of the therapeutic effects of ATARAXOID is noted by Warter*: "In addition it was possible in many cases for the first time to gain the active cooperation of patients in the management of their disease."

INDICATIONS: Rheumatoid arthritis; other collagen diseases and related conditions; other musculoskeletal disorders (myositis, fibrositis, bursitis, etc.); allergic states, including chronic bronchial asthma and severe hay fever; and allergic/inflammatory diseases of the skin and eyes.

ADMINISTRATION AND DOSAGE: ATARAXOID dosage varies with individual response. Clinical experience suggests the following daily dosage: Initial therapy—4-6 ATARAXOID 5.0 Tablets. Maintenance—1-4 ATARAXOID 5.0 Tablets or 2-8 ATARAXOID 2.5 Tablets. After initial suppressive therapy, gradual reduction of prednisolone dosage should begin and continue until the smallest effective dose is reached. Prescribe in divided doses, after meals and at bedtime.

SIDE EFFECTS: Prednisolone may produce all of the side effects common to other corticosteroids. As with other corticosteroids, insomnia, mild hirsutism, moonface and sodium retention have occurred. Osteoporosis may develop after long-term corticosteroid therapy.

PRECAUTIONS AND CONTRAINDICATIONS: Usual corticosteroid precautions should be observed. Incidence of peptic ulcer may increase on long-term prednisolone therapy. However, therapy has often been maintained for long periods without adverse effects. Contraindicated in infectious disease including active tuberculosis (except under close supervision), peptic ulcer, certain infections of the cornea, such as dendritic keratitis, superficial punctate keratitis, epidemic keratoconjunctivitis, and in patients with emotional instability. Caution is indicated in the treatment of diabetic patients and patients with severe cardiovascular disease, and in some cases sodium restriction and potassium supplementation must be considered.

SUPPLIED: As green, scored ATARAXOID 5.0 Tablets, containing 5 mg. prednisolone and 10 mg. hydroxyzine hydrochloride and blue, scored ATARAXOID 2.5 Tablets, containing 2.5 mg. prednisolone and 10 mg. hydroxyzine hydrochloride.

More detailed professional information available on request.

*Warter, P. J.: Prednisolone-hydroxyzine combination in rheumatoid arthritis, J. M. Soc. New Jersey 54:7, 1957.



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Division, Chas. Pfizer & Co., Inc. Brooklyn 6, New York

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ATARAXOID

PREDNISOLONE-HYDROXYZINE HCI
CORTICOSTEROID-ATARACTIC





The Clinical Study:1

38 patients, male and female, all of whom gained weight on a previous diet regimen.

The Rx:

Desoxyn Gradumet, 10 or 15 mg., once daily, in the morning.

The Clinical Result:

The entire group averaged a weight loss of 15 pounds between two and 12 months of treatment. Eight women, weighing between 178 and 269 pounds, took Desoxyn for six months. They averaged a loss of 34 pounds. The heaviest

woman lost 57 pounds, while another lost 71 pounds.

All the results weren't good, of course. One male actually gained seven pounds after four months. And there were two other patients whose weight remained unchanged after four and six months of treatment.

A Sidelight:

The clinician noted that there was an occasional finding of tablets in stools. He wrote: "A certain doubt existed in our minds that this residual tablet did not contain amphetamine. We arranged



for analysis for four of such tablets in patients taking 15 mg. and found that in each instance, there was no trace of amphetamine."

The Conclusion:

"Desoxyn has the best patient acceptance of any of the medications we have used as an appetite suppressant... It is our impression that Desoxyn Gradumet does slowly release amphetamine and thus, reduce side effects that are a problem. It is likewise our impression that the medication is a definite aid in weight reduction and has a high patient acceptability. We are at present using

this drug in our practice as a routine adjutant to a weight reduction program."

1. Cole, R. E., Communication to Medical Department, Abbott Laboratories, 1961.

The Drug:

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All-Day Appetite Control from a Single Oral Dose—5, 10 or 15 mg.



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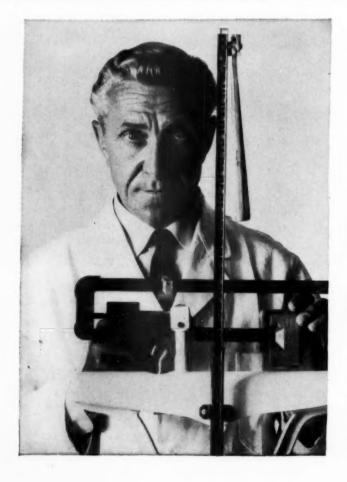
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Can we measure the patient's comfort?

Not objectively, as body weight can be measured on a scale.

The higher level of relief reported with this new corticosteroid is a subjective thing that must be seen, by you, in your own patients.

Alphadrol*

Upjohn
75th year

See page 127 for description, indications, dosage, precautions, side effects, and how supplied.

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When the stomach has a nervous patient!

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antispasmodic/sedative

relaxes the tense patient and his jittery stomach...without the sedative "build-up" many patients experience with phenobarbital preparations.

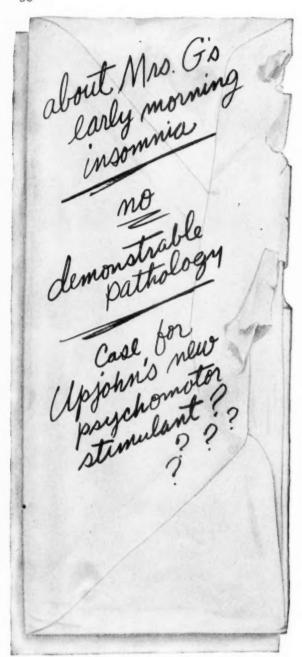
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SEE PAGE 42-43

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Bloating, belching, borborygmus or flatulence—whatever the symptoms of gastrointestinal gas, Phazyme provides uniquely effective relief. Phazyme is the first comprehensive treatment for gastrointestinal gas that combines both digestive enzymes and gas-releasing agents—dual action that provides far better results than either agent alone. Digestive enzymes minimize gas formation resulting from digestive disorders or food intolerance. The gas-releasing agent, specially activated dimethyl polysiloxane, breaks down gas-enveloping membranes—prevents gas entrapment. A two-phase tablet,

Phazyme releases these active components in the environments best suited to their actions—stomach or small intestine.

Phazyme is ideal medication for relieving gas distress in patients on the currently popular 900-calories-a-day diet. It is also recommended as routine therapy for cardiac patients to prevent gas from aggravating, complicating or simulating angina.

DOSAGE: One tablet with meals and upon retiring, or as required. SUPPLIED: As two-phase release, pink tablets, in bottles of 50 and 100.

REED & CARNRICK / Kenilworth, New Jersey

minimizes gas formation • prevents gas entrapment

PHAZYME TABLETS

When anxiety adds to the gas problem —

Phazyme with Phenobarbital The Phazyme formula with 1/4 gr. phenobarbital. Supplied In bottles of 50. Phenobarbital may be habit forming.

Stress Conditions and Citrus Bioflavonoid Therapy

Capillary damage — increased permeability — is a uniform basic reaction resulting from injury or stressors of various types:

NUTRITIONAL: Malnutrition, toxins, pregnancy, growth.

ENVIRONMENTAL: Temperatures, pressure, radiation, allergies.

DISEASE STATES: Viral, bacterial, malignancies, endocrine.

The multiple activities of the citrus bioflavonoids in the prevention or reversal of the inflammatory process include: (1) Maintenance of capillary integrity, (2) In cellular metabolic processes, by potentiating corticosteroids, vitamins and essential nutrients, and by inhibition of hyaluronidase, and (3) Direct anti-inflammatory action.

In the treatment of stress conditions include the citrus bioflavonoids (Lemon Bioflavonoid Complex, Hesperidin Complex and Hesperidin Methyl Chalcone) in the therapeutic regimen.

FREE: Write for "CITRUS BIOFLAVONOIDS in health and disease"—the comprehensive Sunkist brochure reviewing current bioflavonoid research.



Behind leading labels:

Specialty formulations of leading pharmaceutical manufacturers contain Sunkist® Brand Citrus Bioflavonoids.





an oxazine... not an amphetamine

Unsurpassed Effectiveness

In all controlled clinical studies, Preludin has produced impressively greater weight loss than placebo tablets regardless of the degree of enforcement of dietary restriction.

Exceptionally High Tolerance
Reports are numerous of successful use of Preludin in cases intolerant of other anorex-

Flexibility of Dosage

Available as scored tablets of 25 mg. for b.i.d. or t.i.d. administration and also as Endurets®, 75 mg., for once daily administration.



Geigy Pharmaceuticals Division of Geigy Chemical Corporation Ardsley, New York

given to patients with severe hypertension, thyrotoxicosis or acute coronary disease.

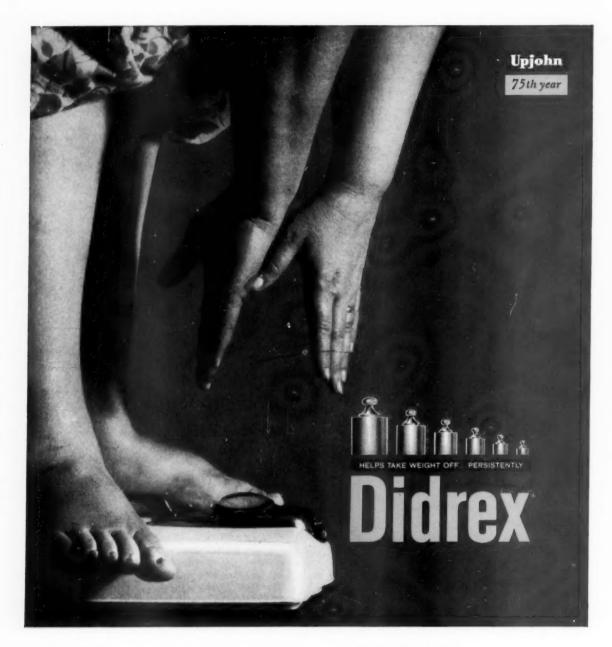
Precautions and Contraindications

Although there have been no reports of significant toxic reactions to Preludin,

on theoretical grounds it should not be

Preludin may be used with caution in cases of moderate hypertension and cardiac decompensation.

Preludin®, brand of phenmetrazine hydrochloride. Under license from C. H. Boehringer Sohn, Ingelheim



Didrex doesn't perform miracles... it just helps the obese patient do

it herself. The reason is simple: persistent, significant loss of weight, up to 30 weeks in reported cases, helps to preclude the "weight plateau" that so often discourages dieters after a few weeks. Thus, time and will become your allies in changing the patient's dietary habits built over months or years of weight accumulation. Didrex may be used in closely supervised diabetic, coronary insufficient, and hypertensive patients.

BRIEF BASIC INFORMATION

Description: Didrex is the Upjohn brand of benzphetamine hydrochloride[(+)-N-benzyl-N, a-dimethyl-phenethylamine hydrochloride]. A sympathomimetic compound with marked anorectic action and relatively little stimulating effect on the CNS or cardiovascular system.

indications: Control of exogenous obesity.

Contraindications: None known to date. However, use with caution in moderate or severe hypertension, thyrotoxicosis, acute coronary disease, or cardiac decompensation.

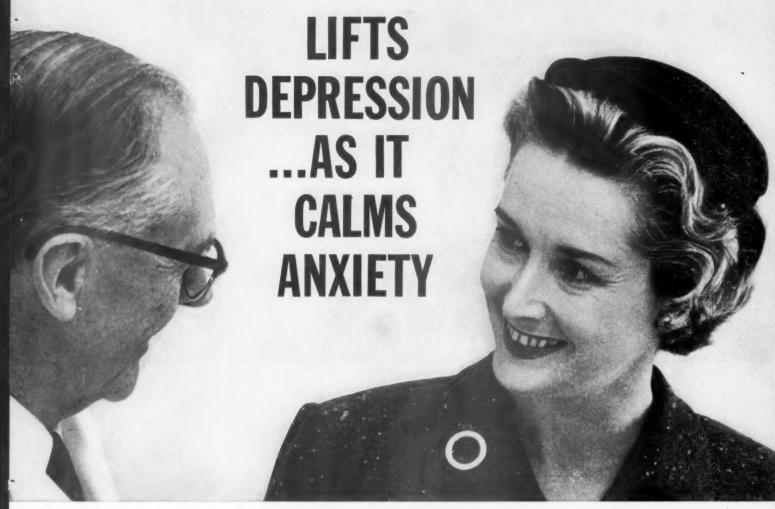
Dosage: Initiate appetite control, for several days, with one 25 or 50 mg. tablet in mid-morning or mid-afternoon, according to the patient's eating habits. Then "adjust" dosage to suit each patient's needs to a maximum of 150 mg. daily.

Side Effects: No effects on blood, urine, renal or hepatic functions have been noted. Minimal side effects have been observed occasionally: dry mouth, insomnia, nausea, palpitations and nervousness.

Supplied: 25 mg, and 50 mg, (scored), benzphetamine hydrochloride, press-coated tablets, in bottles of 100; 50 mg, tablets are also available in bottles of 500.

*Trademark-brand of benzphetamine hydrochloride, Upjohn.

References: 1. Stough, A. R.: Weight loss without diet worry: use of benzphetamine hydrochloride (Didrex). Journal of the Oklahoma State Medical Association, 53:760-767 (November) 1960. 2. Oster, H., and Mediar, R.: A clinical pharmacologic study of benzphetamine (Didrex), a new appetite suppressant. Arizona Medicine, 17:398-404 (July) 1960. 3. Simkin, B., and Wallace, L.: A controlled clinical trial of benzphetamine (Didrex). Current Therapeutic Research, 2:33-38 (February) 1960.



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Brightens up the mood, brings down tension

Deprol's balanced action avoids "seesaw" effects of energizers and amphetamines. While energizers and amphetamines may stimulate the patient-they often aggravate anxiety and

And although amphetamine-barbiturate combinations may counteract excessive stimulation they often deepen depression and emotional fatigue.

These "seesaw" effects are avoided with Deprol. It lifts depression as it calms anxiety - a balanced action that brightens up the mood, brings down tension, and relieves insomnia, anorexia and emotional fatigue.

Acts rapidly - you see improvement in a few days. Unlike the delayed action of most other antidepressant drugs, which may take two to six weeks to bring results, Deprol relieves the patient quickly - often within a few days. Thus, the expense to the patient of long-term drug therapy can be avoided.

Compatible with therapy for physical diseases. Deprol can be used safely with specific therapies for cardiovascular, G.I. and upper respiratory conditions. It does not cause liver damage, hypotension or tachycardia.

'Depro

Dosage: Usual starting dose is 1 tablet q.i.d. When necessary, this may be increased gradually up to 3 tablets q.i.d. With establishment of relief, the dose may be reduced gradually to maintenance levels.

Composition: 1 mg. 2-diethylaminoethyl benzilate hydro-chloride (benactyzine HCI) and 400 mg. meprobamate. Supplied: Bottles of 50 light-pink, scored tablets. Write



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a superior antihistamine with minimal side effects a combination
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for effective
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an effective, safe expectorant to increase respiratory tract fluid a reliable cough suppressant for those patients who need added potency

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Phlebothrombosis of femoral and iliac vein, 3 weeks after onset.

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Superior vena cava thrombosis (8 hrs. after starting THROMBOLYSIN).





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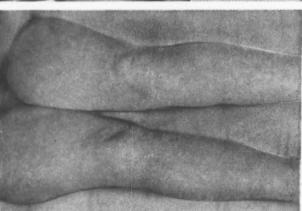




After 6 days' therapy.

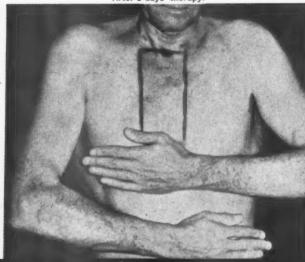






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THROMBOLYSIN makes possible

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Supply: Each bottle contains 50,000 MSD units.

*See package circular for qualifications concerning cerebrovascular accidents and myocardial infarction.

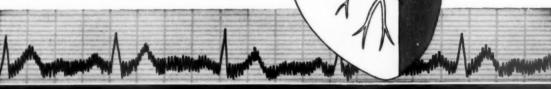
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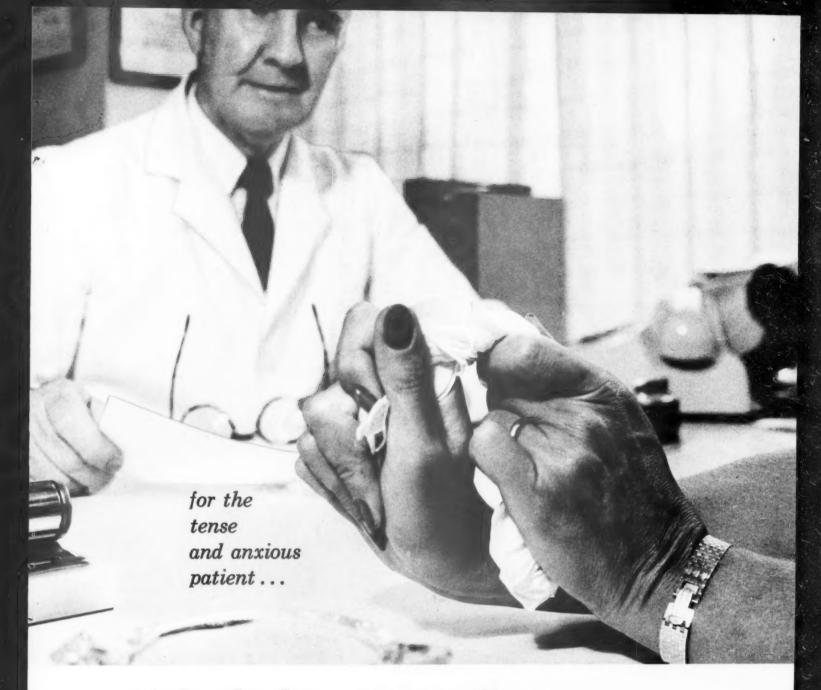
"If one digitalis agent were to be recommended for its adaptability to the many and varied clinical contingencies, we believe Digoxin would be the drug of choice."

Lown, B., and Levine, S. A.: Current Concepts in Digitalis Therapy, Boston, Little, Brown & Company, 1954, p. 23, par. 2.

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a sustained-release tranquilizer that does not cause autonomic side reactions

- WELL TOLERATED, CONTINUOUS RELIEF of anxiety and tension for 12 hours with
 just one capsule without causing autonomic side reactions and with little or no
 impairment of mental acuity, motor control or normal behavior.
- ECONOMICAL for the patient—daily cost is only a dime or so more than for barbiturates.

Meprospan-400

400 mg. meprobamate (Miltown®) sustained-release capsules

Usual dosage: One capsule at breakfast lasts all day; one capsule with evening meal lasts all night.

Available: Meprospan-400, each blue-topped capsule contains 400 mg. Miltown (meprobamate).

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tense
and
nervous
patient

Miltown is a *known* drug and a dependable friend. Its few side effects have been fully reported. *There are no surprises in store for either the patient or the physician*. This is why, despite the appearance of "new and different" tranquilizers, meprobamate (Miltown) is prescribed more often than any other tranquilizer in the world.

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- 2 does not produce ataxia
- 3 no cumulative effects in long-term therapy
- 4 does not produce Parkinson-like symptoms, liver damage or agranulocytosis
- 5 does not muddle the mind or affect normal behavior

Miltown®

Usual dosage: One or two 400 mg. tablets t.i.d.

Supplied: 400 mg. scored tablets, 200 mg. sugar-coated tablets;
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Butazolidin Geigy

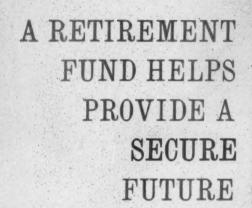
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Because they are a reliable source of vitamins, minerals, hormones, and digestive enzymes, ELDEC Kapseals may help to check certain dietary and hormone deficiencies ...favorably influence your patient's current and future status of health.

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Packaging: FIDEC Kapseals are available in bottles of 100.

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HYCOMINE Syrup

THE COMPLETE Rx FOR COUGH CONTROL

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relieves cough and associated symptoms in 15-20 minutes ■ effective for 6 hours or longer ■ promotes expectoration ■ rarely constipates ■ agreeably cherry-flavored

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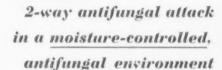
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first <u>topical</u> fungicide with sweat-inhibiting action*



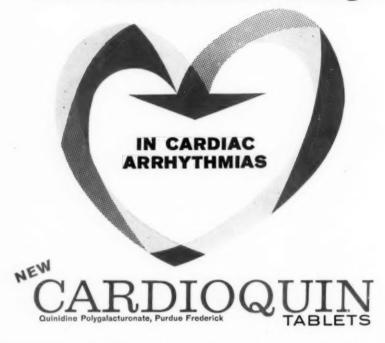




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ONLY ONE 'CARDIOQUIN' TABLET B.I.D. is the typical maintenance dosage in the treatment of arrhythmias. This, and other outstanding clinical advantages of 'Cardioquin' therapy are inherent in the new quinidine molecule—quinidine polygalacturonate:

- ★ The quinidine ion assures

 FULL QUINIDINE CARDIODYNAMICS¹-5
- ★ The polygalacturonate moiety controls quinidine release...affords VIRTUAL FREEDOM FROM GASTROINTESTINAL DISTRESS¹-3
- Absence of "peaks and valleys" permits SMOOTH CONVERSION TO NORMAL SINUS RHYTHM^{1,3}

NOTE: In conversion of arrhythmias, 'Cardioquin' Tablets may be substituted for conventional quinidine salts on the tablet-fortablet basis, each 'Cardioquin' Tablet containing 275 mg. of quinidine polygalacturonate, equivalent to 3 grains (200 mg.) of
quinidine sulfate. To prevent recurrence of arrhythmias, one 'Cardioquin' Tablet may be administered two or three times daily.

Maintenance requirements will vary with the individual patient's needs, but a dosage of one tablet morning and night will generally be adequate as a starting maintenance regimen. Indications and contraindications are the same as for other quinidine
preparations. Detailed instructions as to dosage and administration, as well as complete bibliography, are available on request.

SUPPLY: Uncoated, scored tablets in bottles of 50.

REFERENCES: 1. Tricot, R., Nogrette, P.: Presse med. 68:1085 (June 4) 1960. 2. Schwartz, G.: Angiology 10:115 (April) 1959. 3. Shaftel, N., Halpern, A.: Am. J. Med. Sci. 236:184 (Aug.) 1958. 4. Pote, H. H.: Angiology 12:320 (July) 1961. 5. Orgain, E. S.: Progress in Cardiovasc. Dis. 2:663 (May) 1960.

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Each ROBAXISAL Tablet contains:

ROBAXIN (methocarbamol Robins) 400 mg. Acetylsalicylic acid (5 gr.)........... 325 mg.

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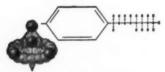
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Why is the methyl "governor" in Orinase SO important?

One of the most significant advantages of Orinase therapy is the rarity of associated hypoglycemic reactions.

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As a result of the oxidation of its methyl group, Orinase shows a decline in activity soon after it reaches its effective peak in the plasma. Maintenance dosage serves to reduce blood sugar levels to normal, but rarely below that point, and there is no reported problem of accumulation.



An exclusive methyl "governor" minimizes hypoglycemia

Indications and effects: The clinical indication for Orinase is stable diabetes meilitus. Its use brings about the lowering of blood sugar; glycosuria diminishes, and such symptoms as pruritus, poly-uria, and polyphagia disappear.

uria, and polyphagia disappear. Dosage: There is no fixed regimen for initiating Orinase therapy. A simple and effective method is as follows: First day—6 tablets, zecond day—4 tablets; third day—2 tablets. The daily dose is then adjusted—raised, lowered or maintained at the two-tablet level, whichever is necessary to maintain optimum control.

maintain optimum control.

Patients receiving insulin (less than 20 units)—
discontinue insulin and institute Orinase; (20 to
50% reduction in insulin dose with a concurrent 30
to 50% reduction in insulin dose with a further
careful reduction as response to Orinase is observed; (more than 40 units)—reduce insulin by
20% and initiate Orinase with a further careful
reduction in insulin dosage as response to Orinase
is observed. In candidates for combined Orinaseinsulin therapy, an individualized schedule is usually obtainable during a trial course of two or
more weeks.

Contraindications and side effects: Orinase is Contraindicated in patients having juvenile or growthonset, unstable or brittle types of diabetes
melitus; history of diabetic coms, fever, severe
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Side effects are mild, transient and limited to an

Side effects are mild, transient and limited to approximately 3% of patients. Hypoglycemia and toxic reactions are extremely rare. Hypoglycemia is most likely to occur during the period of transition from insulin to Orinsse. Other untoward Copyright 1961, The Upjohn Company

reactions to Orinase are usually not of a serious nature and consist principally of gastrointestinal disturbances, headache, and variable allergic skin manifestations. The gastrointestinal disturbances (nausea, epigastric fullness, heartburn) and headache appear to be related to the size of the dose, and they frequently disappear when dosage is reduced to maintenance levels or the total daily dose is administered in divided portions after meals. It is administered in divided portions after meals in administered in divided portions after meals. The mean and urticartal, morbilliform, or maculopapular eruptions) are transient reactions, which frequently disappear with continued drug administration. However, if the skin reactions persist, Orinase should be discontinued.

Orinase should be discontinued.
Clinical toxicity: Orinase appears to be remarkably free from gross clinical toxicity on the basis of experience accumulated during more than four years of clinical use. Crystalluris or other untoward effects on renal function have not been observed. Long-term studies of hepatic function in humans and experience in over 650,000 disbetics have shown Orinase to be remarkably free of hepatic toxicity. There has been reported only one case of cholestatic jaundice related to Orinase administration, which occurred in a patient with pre-existing liver disease and which rapidly reversed upon discontinuance of the drug.

Each tablet contains:

Each tablet contains: Tolbutamide 0.5 Gm. Supplied: In bottles of 50.

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Supplied: as 0.75 mg, and 0.5 mg, scored, pentagon-shaped tablets in bottles of 100. Also available as Injection DECADRON Phosphate and new Elixir DECADRON. Additional information on DECADRON is available to physicians on request. DECADRON is a trademark of Merck & Co., Inc.

Reference: 1. Bunim, J. J., in Hollander, J. L.: Arthritis and Allied Conditions, ed. 6, Philadelphia, Lea & Febiger, 1960, p. 364.



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Decadron &

Natural History of Pyelonephritis

"Pyelitis" of Infancy Cystitis"

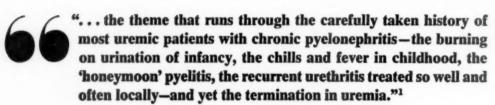
Symptomatic

Level of Symptomatology

Inapparent Active

Healed

AGE (years) 10 20





at every age of life...at every stage of infection

Urinary tract infections of childhood are frequent, persistent and difficult to cure. If inadequately treated, serious sequelae in later life are too often the result. The childbearing age represents a second major stage for urinary tract infection, a hazard to both mother and fetus, and a potential precursor of renal insufficiency if not thoroughly eradicated. During the middle and later years relapse and reinfection, with the spectre of renal failure, make management a grave problem—preserving function and prolonging life become the realistic therapeutic goals.

"Pyelitis" of Pyelonephritis Asymptomatic Bacteriuria Hypertension LV Failure

Furadantin

40

50

30

prompt = thorough = dependable = safe = economical control of infection throughout the urinary system

"... seems to be by far the most effective drug to be employed, and this has been substantiated in practice. It is a drug of low toxicity and, what is more important, bacteria rarely if ever become resistant to it. It can be employed for long periods of time, is bactericidal and does not favor the appearance of monilial infections." ²

Average Furadantin Adult Dosage: 100 mg. tablet q.i.d. with meals and with food or milk on retiring. For acute, uncomplicated infections, 50 mg. may be administered. If improvement does not occur in 2 or 3 days, increase the dose to 100 mg. q.i.d. Supplied: Tablets, 50 mg. and 100 mg. Oral Suspension, 25 mg. per 5 cc. tsp.

1. Birchall, R.: Am. Practit. 11:918, 1960. 2. Sanjurjo, L. A.: Med. Clin. N. Amer. 43:1601, 1959. Complete information in package insert or on request to the Medical Director.

EATON LABORATORIES, Division of The Norwich Pharmacal Company, NORWICH, NEW YORK

measurable benefits in edema and hypertension





plus more built-in potassium protection than any other diuretic-antihypertensive

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50/1000 Tablets

Supplied: ESIDRIX-K 50/1000 Tablets (white, coated), each containing 50 mg. Esidrix and 1000 mg. potassium chloride (equivalent to 524 mg. potassium).

Also available: ESIDRIX-K <u>25/500 Tablets</u> (off-white, coated), each containing 25 mg. Esidrix and 500 mg. potassium chloride. ESIDRIX <u>Tablets</u>, 50 mg. (yellow, scored) and 25 mg. (pink, scored).

For complete information about Esidrix and Esidrix-K (including dosage, cautions, and side effects), see current Physicians' Desk Reference or write CIBA, Summit, N. J.

ESIDRIX● (hydrochlorothiazide CIBA) SINGOSERP● (syrosingopine CIBA)

C I B A Summit, N. J.

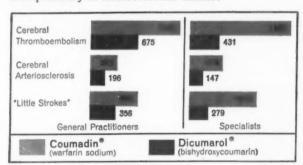
Nationwide Survey Explores Current Use of Anticoagulants in Cerebrovascular Disease

It has been estimated that there are 2,000,000 people suffering from vascular disease of the brain in the United States, and that each year at least 500,000

persons are incapacitated by some kind of cerebral accident.² With the advancing age of our population, this problem is likely to increase.

As reported in previous numbers of this series, Endo Laboratories received replies to its comprehensive Anticoagulant Survey from a total of 10,016 physicians across the nation. Among the questions asked were — Are you now using oral anticoagulants for cerebral thromboembolism, cerebral arteriosclerosis, or "little strokes"—therapeutically, prophylactically? Without regard to the anticoagulant chosen, 14.4% of physicians reported use of oral anticoagulation in therapy of cerebral arteriosclerosis, 27.9% in little strokes, and 46.9% in cerebral thromboembolism. Anticoagulation was used prophylactically as follows: 10% in cerebral arteriosclerosis, 16.8% in little strokes, and 21.2% in cerebral thromboembolism.

Comparison of usage was also made among the 61.4% of reporting physicians prescribing Coumadin® most often and the 27.6% using Dicumarol®. (The remainder used indandiones [1.9%] and other anticoagulants.) The following graph shows the application of the leading anticoagulants therapeutically in cerebrovascular disease:



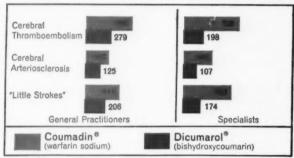
Physicians Using Oral Anticoagulation Therapeutically in Cerebrovascular Disease

Specialists Lead in Therapeutic Application of Anticoagulants

The analysis of the data presented in this survey indicates that 57% of the cardiologists and internists prescribing Coumadin—the most frequently prescribed oral anticoagulant—and 42% of the general practitioners used the drug therapeutically in cerebral thromboembolic disease. It is also noteworthy that 39% of the specialists used Coumadin in therapy of "little strokes" as compared with 22% of the

general practitioners. Less frequent was its use as part of the therapy of cerebral arteriosclerosis—18% among the specialists and 12% among the general practitioners.

Anticoagulation was used less often for prophylaxis than for therapy of cerebral thromboembolism, little strokes, or cerebral arteriosclerosis, as shown in the following graph:



Physicians Using Oral Anticoagulation Prophylactically in Cerebrovascular Disease

Indications According to Recent Clinical Reports

Clinical experience emphasizes the need for careful diagnosis and patient selection before using anticoagulants in cerebral vascular disorders. Authorities are generally agreed that anticoagulants help to minimize the occurrence of attacks in patients with transient ischemic episodes, 3.6 which are "far more common than was previously suspected." In addition, anticoagulation is advocated in the slowly evolving stroke, 5.7 i.e., "slow-onset" infarction. Evidence in cases of cerebral embolism indicates that anticoagulants may reduce the mortality rate. In patients with completed cerebral infarction, the findings of Thomes indicate that long-term anticoagulant therapy may be valuable in minimizing recurrences and mortality rate. His results also suggest that "there is no time when it becomes safe to discontinue anticoagulant therapy." Since the source of cerebral dysfunction may lie in occlusive disease of the carotid arteries in the neck, cerebral angiography is recommended as a valuable means of establishing the diagnosis. 1.2

Physicians choosing Coumadin for anticoagulation have reportedly done so (see No. 1 of this series) because of its predictable effect, ease of maintenance, and single daily dose which permit a smoother, more convenient, and less hazardous anticoagulant regimen.

Meyer, J. S.: Am. J. Med. 30:577, 1961.
 Kuhn, R. A.: Current M. Digest 28:51, 1961.
 Groch, S. N., and Wright, I. S.: Circulation 23:458, 1961.
 Siekert, R. G.; Millikan, C. H., and Whisnant, J. P.: J.A.M.A. 176:19, 1961.
 Carter, A. B.: Neurology 11:801, 1961.
 Groch, S. N.: Ibid., p. 141.
 Thomes, A. B.: Minnesota Med. 42:1587, 1959.

Another professional service of Endo Laboratories-makers of

COUMADIN[®]

the proven anticoagulant for long-term maintenance

FOR ORAL, INTRAVENOUS OR INTRAMUSCULAR USE

Coumadin (warfarin sodium) is manufactured under license from the Wisconsin Alumni Research Foundation, and is supplied as scored tablets of 2 mg., lavender; 2½ mg., orange; 5 mg., peach; 7½ mg., yellow; 10 mg., white; and 25 mg., red, as well as in 50 mg. and 75 mg. single-injection units.



ENDO LABORATORIES Richmond Hill 18, New York



this is PLEXONAL

(ACTUAL SIZE AND SHAPE)

Optimum results are obtained by gradually increasing the dosage to the maximum the patient can tolerate without the appearance of drowsiness. The following procedure for dosage adjustment has proven highly successful: Take one tablet 2 times per day for 2 days. On the third day increase the daily dosage by one tablet. Similarly increase the dose every third day thereafter, to the point of drowsiness.

For example, if one tablet 4 times a day produces an obvious aleepy feeling, and on three the patient is comfortable, then the proper dose will be three tablets per day.

a superior daytime relaxing agent

(NOT A TRANQUILIZER)

Comparative clinical studies show that PLEXONAL is superior to meprobamate or barbiturates for daytime relaxation"

"Plexonal was preferred (superior therapeutic effect) by 73.7 per cent of the patients, whereas 11.1 per cent preferred meprobamate, a ratio of 6.6 to 1.... 30.5 per cent noted adverse reactions to meprobamate as compared to 7 per cent in respect to Plexonal.... Plexonal gave better results than did any of the sedative or relaxing agents that have been available during our experience covering the previous 15 years."

In 26 older age cardiac patients, "A comparison of Plexonal with the therapy previously employed showed that 17 did better on Plexonal than on meprobamate, 6 did better on meprobamate than on Plexonal and 3 responded the same to both."2

Indications: Anxiety, tension, apprehension, nervousness, irritability, restlessness, hyperexcitability.

Extremely well tolerated by geriatric patients who need mild sedation, as well as by depressed patients.

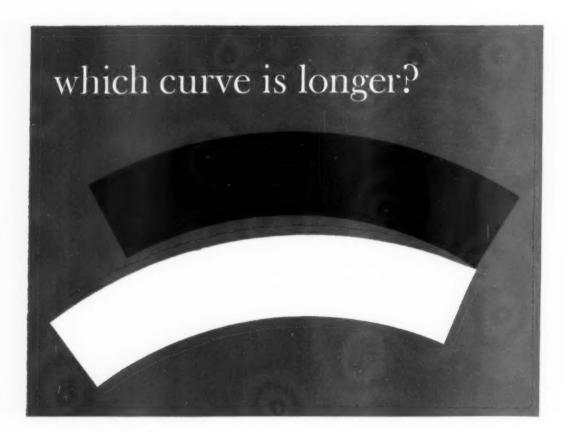
Dosage: One tablet 3 or 4 times a day is adequate for most patients. However, some require up to six tablets per day, whereas others respond adequately to as little as 1 tablet per day?

Composition: Each tablet contains sodium diethylbarbiturate 45 mg., sodium phenylethylbarbiturate 15 mg., sodium isobutylallylbarbiturate 25 mg., scopolamine hydrobromide 0.08 mg., dihydroergotamine methanesulfonate 0.16 mg.

1. Scheifley, C. H.: Proc. Staff Meet. Mayo Clin. 34:408 (Aug. 19) 1959.

2. Davanloo, H.: Am. J. of Psychiat. 117:740 (Feb.) 1961.





Fascinating . . . how one curved figure seems to be longer than the other—even when you know they're both the same.

Two oral penicillins can be just as difficult to compare. If only the price of the drugs were to be considered, the choice would be clear. But isn't it what a drug does that counts?

V-Cillin K® achieves two to five times the serum levels of antibacterial activity (ABA) produced by oral penicillin G.¹ Moreover, it is highly stable in gastric acid and, therefore, more completely absorbed even in the presence of food. Your patient gets more dependable therapy for his money . . . and it's therapy—not tablets—he really needs.

For consistently dependable clinical results prescribe V-Cillin K in scored tablets of 125 and 250 mg. V-Cillin K, Pediatric, in 40 and 80-cc.-size packages. Each 5 cc. (approximately one teaspoonful) contain 125 mg. (200,000 units) penicillin V as the crystalline potassium salt.

V-Cillin K* (penicillin V potassium, Lilly)
1. Griffith, R. S.: Antibiotic Med. & Clin. Therapy, 7:129, 1960.



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Product brochure available; write Eli Lilly and Company, Indianapolis 6, Indiana.

The American Journal of Medicine

Vol. XXXI

NOVEMBER 1961

No. 5

Editorial The Plasmocytic Dyscrasias

Plasma Cell Myeloma and Primary Macroglobulinemia

PLASMA cell myeloma and Waldenström's macroglobulinemia are presently considered to represent dyscrasias originating in the antibody-producing cell lines of the reticuloendothelial system. In accordance with the hypothesis of Burnet [1], it is currently presumed that the antibody-producing apparatus consists of a complex of specific cell populations or clones, each of which is responsible for the elaboration of a single, or very limited number [2] of immune globulins. The Burnet hypothesis further suggests that the majority of these clones are "non-selected," and accordingly, if they produce any protein, it is protein without functional (antibody) specificity. A finite number of clones, however, are "selected" in the course of an individual's life by virtue of exposure to specific antigens. Following primary antigenic challenge, an individual clone becomes "selected" to produce a specific antibody, and subsequent exposure to the same antigen (secondary antigenic challenge) results in enhanced production of this antibody by the specific cell family. It appears, however, that the response of the reticuloendothelial system to an antigenic challenge is only in small part a specific response, since but a minute fraction of the gamma globulin increment which results from a given antigenic stimulus can be demonstrated to possess antibody specificity by currently available technics. Of course, failure to demonstrate functional specificity in the bulk

of the gamma globulins produced in response to an antigenic challenge may simply reflect methodologic limitations, and perhaps part of this fraction will be shown to be "functional" and "specific" as immunologic technics are advanced.

As schematically diagrammed in Figure 1, the currently available immunochemical and physicochemical data indicate that in the adult three major families of circulating immune globulins are found, exclusive of the components of the complement and properdin systems. Gamma-2, or 7Sy, is the principal constituent of Cohn fraction II, constituting approximately twothirds of the protein within the electrophoretically defined gamma area of serum. Gamma-2 has a molecular weight of 160,000 and contains the majority of the acquired antibacterial and antiviral antibodies. Although the electrophoretic maximum of this fraction is in the slow gamma or gamma-2 region, it is established that the anodal boundary extends through the beta, and into the alpha-2 mobility region. The carbohydrate content of γ_2 is approximately 3 per cent, as compared to the carbohydrate content of the second family of immunoglobulins, designated gamma₁A, which is significantly higher (10 to 11 per cent). The carbohydrate-rich gamma₁A fraction has a slightly greater mean electrophoretic mobility than gamma-2, but its sedimentation constant is the same as gamma-2, i.e., 7Sγ, corresponding to a

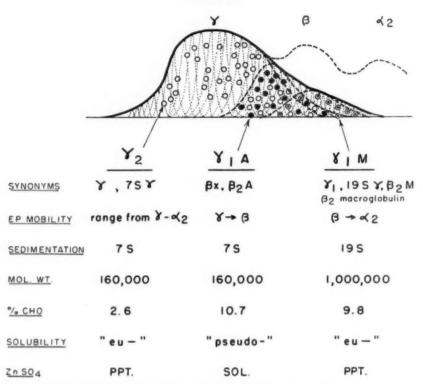


Fig. 1. Schematic representation of the immunoglobulins of normal human serum. γ_2 constituents are indicated by \bigcirc , $\gamma_1 A$ by \bigcirc , $\gamma_1 M$ by \bigcirc . From Osserman, E. F. and Lawlor, D. P. Ann. New York Acad. Sc., 1961 [12].

molecular weight of 160,000. Diphtheria and tetanus toxin antibodies, typhoid-O agglutinins and paratyphoid-B antibodies have been identified as belonging to the gamma₁A immunoglobulin family. The third family of immune globulins, designated gamma₁M, is comprised of the 19S macroglobulins with a molecular weight of the order of 1,000,000. The gamma₁M fraction, like gamma₁A, has a high carbohydrate content (10 to 11 per cent), and in this fraction the isohemagglutinins, Rh antibodies, cold agglutinins and rheumatoid factor have been identified.

As noted in Figure 1, several nomenclature systems have been applied to the three immunoglobulin fractions. Indeed, the designations beta₂A and beta₂M, for gamma₁A and gamma₁M, respectively, initially introduced by Grabar and co-workers [3], are still in frequent use. More recently, however, it has been agreed to employ the term "gamma" as a common root because of the association through usage of "gamma globulin" with the immunoproteins, but the "extragamma" electrophoretic spread of these three families of proteins must be borne in mind.

The comprehensive immunochemical studies of Grabar [3], Heremans [4], Kunkel [5], Franklin [6], Korngold [7] and others have established that each of the three immunoglobulin fractions (γ_2 , $\gamma_1 A$ and $\gamma_1 M$) shares certain antigenic (structural) determinants with the other two, and at the same time possesses certain specific groupings. Thus, purified $\gamma_1 A$ and $\gamma_1 M$ will cross react with an anti-γ₂ antiserum, but after absorption with $\gamma_1 A$ and/or $\gamma_1 M$ the anti-y₂ antiserum will still exhibit precipitating activity against the homologous γ_2 fraction. Although to date it has not been possible to define the exact structural units which are shared by the three immunoglobulin fractions, nor, indeed, those which impart their individual antigenic specificities, it is anticipated that this will be accomplished in the not too distant future. In this endeavor the immunochemical and physicochemical studies of enzymatic and chemical fractions of the immunoglobulins which are currently in progress in several laboratories should be of major value.

Despite the extensive cross reactivity of the three immunoglobulin fractions, the technic of immunoelectrophoresis permits their individual

delineation and analysis [3,4]. By this method it has been demonstrated that all three immunoglobulin fractions are increased in the disease states associated with diffuse hypergammaglobulinemia, e.g., cirrhosis, chronic infections, sarcoidosis and the collagen diseases, indicating that a large number of protein-producing clones of the reticuloendothelial system are proliferating, and that a broad spectrum of immunoglobulins is elaborated. Waldenström [8] recently has designated this type of hypergammaglobulinemia "polyclonal gammopathy," in contrast to "monoclonal gammopathies," of which myeloma and primary macroglobulinemia are the prototypes, which appear to represent neoplastic, proliferative disorders (dyscrasias) of single clonal units. The "monoclonal-polyclonal" classification system may ultimately prove to be useful and valid, but it must be borne in mind that its basis is still an hypothesis, and that the "one-clone: one protein theory" has yet to be experimentally established. Indeed, as indicated previously, studies of isolated cell preparations [2] have demonstrated that a single plasma cell may, under certain circumstances, produce two distinct antibodies, although only one protein appeared to be elaborated by the great majority of the isolated single cells in these studies. It is also evident that the array of immunoglobulins formed in certain of the "polyclonal gammopathies," e.g., in rheumatoid arthritis, are quite different from those associated with other diseases in this same general category, e.g., systemic lupus, and with improved serologic and physicochemical technics it should be possible to delineate these differences and to define specific groups of involved clones in specific disease states (? oligoclonal gammopathies) by means of their particular immunoglobulin products.

With respect to the "pathologic" myeloma proteins and macroglobulins, it should be acknowledged that, to date, the issue as to whether these constituents are truly "abnormal," or whether they represent normal components produced in great excess as a consequence of a "monoclonal dyscrasia" has not been resolved. The consistent failure to demonstrate antibody specificity for these proteins despite their established close immunochemical and physicochemical relationships to the normal immunoglobulins has been interpreted as evidence of their "abnormality," but this cannot be accepted as valid since functional specificities have not

been demonstrated for the bulk of the normal immunoglobulins. Likewise, with regard to essentially all the physicochemical and immunochemical data which compare these "paraproteins" with various normal gamma globulin fractions, e.g., Cohn fraction II, the limitations inherent in a comparison of a single protein with a complex mixture of related proteins must be recognized. Accordingly, the designation "paraprotein" is currently employed in order to evade this unresolved "normalcy" issue.

Immunoelectrophoretic analysis of the paraproteins of myeloma and primary macroglobulinemia [4,9–12] has established that approximately 70 per cent of the myeloma serum globulins are immunologically related to γ_2 , and 30 per cent to $\gamma_1 A$, whereas the macroglobulins are all primarily related to the γ₁M immunoglobulin fraction. Significantly, the low molecular weight, Bence Jones urinary proteins have been found to possess both γ_2 and γ_1A immunologic determinants, lending some support to the postulate that these constituents may represent a type of basic sub-unit of the immunoglobulins, synthesized and excreted in excess in myeloma as a consequence of the gross derangements in immunoglobulin production accompanying the neoplastic process [13,14]. Parenthetically, it is of interest that a recent analysis of a low molecular weight, Bence Jones type, urinary protein excreted by a patient with primary macroglobulinemia demonstrated this protein to be immunologically related to the $\gamma_1 M$ fraction, and apparently unrelated to either γ_2 or $\gamma_1 A$. In the current investigations of enzymatic and chemical fractionation products of the immunoglobulins [4,6,15-18] considerable effort is being made to discern structural, chemical or immunologic similarities between specific fragments thus obtained and the Bence Jones proteins. To date, the results of these studies appear to support the thesis that the immunoglobulins are constituted from basic polypeptide sub-units of the Bence Jones type. Edelman and Poulik [16] have indeed speculated that "the primary defect in macroglobulinemia and multiple myeloma may be a failure of specificity and control in production of the various sub-units to form larger molecules"; and that the "Bence Jones proteins may be polypeptide chains that have not been incorporated into the myeloma globulins because of a failure in the linkage phase." Further studies in this area will be of considerable interest.

A wealth of physicochemical and immunochemical evidence has accumulated in recent years [4,5,13,14] which indicates the individual specificity of the macroglobulins, myeloma globulins and Bence Jones proteins from individual patients. Thus, although many structural and immunologic features have been demonstrated to be shared by these three groups of proteins, such as those which have permitted their immunoelectrophoretic groupings, there is an equally formidable body of data which indicate that each patient produces his own unique paraprotein, as evidenced by demonstrated differences in over-all antigenic complement, physical characteristics (electrophoretic mobilities, solubility properties), and chemical constitution (N-terminal and C-terminal amino acids, constituent peptides, carbohydrate content). In addition to providing an exceedingly fertile field for biochemical exploration, this phenomenon of paraprotein individuality has several important clinical implications [19], since it is now possible to relate an ever-increasing number of specific clinical and pathologic manifestations in individual patients to the specific physicochemical properties of the paraproteins elaborated. In this regard, it has been apparent for many years that Bence Jones proteins may cause renal function impairment. Recent evidence suggests that this effect may be the result of a direct protein: protein interaction between certain Bence Jones proteins and renal tubular epithelial cytoplasmic proteins. That a nephrotoxic potential is not common to all Bence Jones proteins is apparent from the clinical fact that Bence Jones proteinuria is not invariably associated with impairment of renal function. The precise structural and chemical groupings responsible for the nephrotoxic effect of particular Bence Jones proteins are still unknown. Likewise, the possibility that the unique proteinaceous infiltrates of selected tissue sites, the so-called para-amyloid or "atypical" amyloid deposits which develop in approximately 10 per cent of cases of overt or occult plasma cell myeloma, may represent similar protein: protein or protein: polysaccharide interactions between the paraproteins, particularly those of the Bence Jones type, and normal tissue constituents has also been suggested [19,20], and recent studies in this laboratory [21] presently appear to support this hypothesis.

Similar clinically significant pathogenic properties of the myeloma serum globulins and of the macroglobulins have also become evident.

Circulatory impairment secondary to increased serum viscosity and/or cold insolubility (cryoglobulins); coagulation defects resulting from the interaction of these paraproteins with specific clotting factors (fibrinogen, factor v, vII, prothrombin) are among the better documented of these effects. There is also evidence that certain serum paraproteins may contribute to the anemia, leukopenia and thrombocytopenia observed in certain of these patients by virtue of binding affinities for the cell membrane constituents of these formed elements (? protein: protein, protein: lipid, or protein: polysaccharide interactions). Elucidation of these and similar phenomena will unquestionably be of clinical value.

The more general use of serum electrophoresis as a routine clinical procedure has unquestionably aided in the diagnosis of myeloma and macroglobulinemia in symptomatic subjects, and is certainly at least partly responsible for the increased frequency with which these diagnoses are being made in almost all clinics. In addition, however, the more widespread routine use of serum electrophoresis has revealed the presence of myeloma-type serum spikes in a small but significant number of completely asymptomatic subjects. Forty of these comprise the present series, of which twenty-four have been previously reported on [22]; Waldenström has described [8] a group of sixty-five similar patients studied in Sweden. Long-term study has established that in a certain percentage of these patients clinically evident myeloma or macroglobulinemia does, in fact, develop after asymptomatic periods of many months or years, but whether this progression will occur in all of this group or whether a truly benign form of "monoclonal gammopathy" exists remains undetermined. Of some interest has been the observation of an unusually high (30 per cent) incidence of carcinomas of diverse types in this group of patients, both in this series and that of Waldenström. Although this may be a purely coincidental association, the possibility of a direct relationship between the gammopathies and these non-plasmocytic neoplasms is under investigation.

It is evident that a number of fundamental issues regarding the elaboration of the immunoglobulins, their structural and immunochemical characteristics and interrelationships, and certain aspects bearing on the pathogenesis and pathophysiology of the clinical disorders of immunoglobulin synthesis have been elucidated

by the numerous, closely integrated clinical and laboratory investigations of recent years. It is equally apparent that truly "key" observations remain to be made.

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Early Recognition and Therapy of Disseminated Coccidioidomycosis*

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With the development of effective antifungal chemotherapy, early and accurate diagnosis of disseminated coccidioidomycosis has become imperative. To be sure, primary pulmonary coccidioidomycosis is usually a benign, self-limited disease, but disseminated coccidioidomycosis has a mortality rate of close to 50 per cent [1].

Previous authors [2-5] have stressed the importance of the following criteria for the purpose of predicting dissemination: (1) Laboratory: continued elevation of erythrocyte sedimentation rate, complement fixation titer of 1:16 or greater. (2) Roentgenograms: persistence of or increasing consolidation of infiltrates, marked mediastinal adenopathy, appearance of infiltrates apically or subapically. (3) Clinical course: continued prostration, weight loss and temperature elevation; appearance of skin test anergy. These criteria have developed primarily from retrospective analyses of cases of disseminated coccidioidomycosis usually observed late in the natural course of the disease. No large series has been reported in which patients with primary pulmonary coccidioidomycosis were followed up from inception of the disease until spontaneous healing or extrapulmonary spread (dissemination) occurred.

In the present study forty-two cases of primary pulmonary coccidioidomycosis were compared with eight simultaneously observed cases of disseminated coccidioidomycosis. It was found that with careful clinical evaluation extrapulmonary spread in coccidioidomycosis could usually be recognized within four weeks of the onset of symptoms. Amphotericin B had its

maximal effectiveness when given early in the course of dissemination.

PATIENT GROUPS

This study consists of fifty patients with coccidioidomycosis observed at Davis-Monthan Air Force Base, Tucson, Arizona, between August 1956 and July 1959. All patients were first seen at military sick call or civilian dependent outpatient clinics.

The diagnosis of primary pulmonary coccidioidomycosis was made in forty-two patients in the presence of one or more of the following criteria: (1) Conversion of coccidioidin 1:100 skin test! within twenty-one days of the onset of symptoms (fifteen patients). A positive test result is one in which induration at least 5 mm. in diameter is measured twenty-four and forty-eight hours after administration. (2) Coccidioidal complement fixation titers of at least 4-plus strength in a 1:2 dilution, but no greater than 1:16; or, coccidioidal precipitin titer of 4-plus strength in any dilution (ten patients). In sixteen patients the major method of diagnosis was skin test conversion and rise in serologic titer. (3) Clinical course (one patient). Other clinically suspected cases were not included because of lack of laboratory confirmation.

Disseminated coccidioidomycosis was diagnosed in eight patients when one or both of the following criteria were met: (1) Maximum coccidioidal complement fixation titer of 1:32 or greater (six of seven patients checked). (2) Isolation of Coccidioides immitis from an extrapulmonary site (seven of seven patients checked). Suggestive growth on Sabouraud's medium was confirmed by mouse inoculation.

For brevity, the primary pulmonary coccidioidomy-cosis group will be referred to as *primary* and the disseminated coccidioidomycosis group as *disseminated*. The high percentage (16 per cent) of disseminated cases in the total group of fifty is not a true reflection

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of the incidence of this form of the disease because many clinically suspected primary cases encountered during the three years of observation were not included. All cases of dissemination seen in that period of time were studied.

The average age in the primary group was twentynine years (range six to fifty) and in the disseminated group was twenty-three years (range nineteen to thirty-two). There was a preponderance of male subjects in both groups (primary: thirty-four; disseminated: seven). Five of the eight disseminated patients were Negro in contrast to only four of forty-two patients with primary pulmonary disease. A definite history of excessive dust exposure was obtained in six disseminated patients but only in nine of the forty-two patients with primary pulmonary disease. This apparent difference may be due to more vigorous questioning of the former group during prolonged hospitalization. Patients in the primary group had lived in an area endemic to coccidioidomycosis for an average of twenty-eight months (range one to 132 months); those in the disseminated group for an average of thirteen months (range four and a half to thirty months). The large number of patients and the wide range in the primary group may account for this difference.

The two groups were further studied in respect to symptoms, physical examinations, laboratory tests taken on admission, clinical course, roentgenograms and therapy. Patients in the primary group were followed up to fifty-two weeks and the seven surviving patients in the disseminated group for forty to 155 weeks after initial hospitalization. All but two patients in the primary group were followed up for four weeks or longer. In the primary group the time of onset of disease was usually assumed to be the first day of chest pain. The relative infrequency of this complaint in the disseminated group (vide seq.) made it more difficult to date the onset of disease; for this reason the first day of hospitalization was taken as day 1.

Table 1
PHYSICAL FINDINGS ON ADMISSION IN FIFTY CASES
OF COCCIDIOIDOMYCOSIS

Primary 2 cases)	Dis- seminated
,	(8 cases)
100.3	102
34	1
5	2
4	0
0	1
0	1

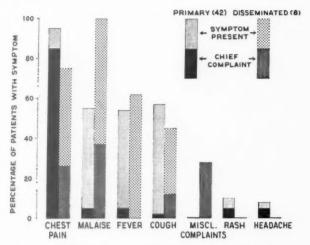


Fig. 1. Predominant symptoms in fifty cases of coccidioidomycosis.

RESULTS

Findings on Admission. Similar complaints prompted hospitalization in both groups. (Fig. 1.) Chest pain, usually pleuritic, was the chief complaint in a large number of the patients with the primary form of the disease. Weight loss and prolonged symptoms prior to hospitalization were prominent in the disseminated group. Except for the frequency of chest splinting or pleural rub in the primary group, the physical findings were similar in both groups and no remarkable differences could be found between routine laboratory values obtained on admission. (Tables I and II.) The mean total leukocyte

Table II
AVERAGE LABORATORY VALUES ON HOSPITAL
ADMISSION IN FIFTY CASES OF
COCCIDIOLOMYCOSIS

	Coccidioidomycosis			
Laboratory Values	Primary (42 cases)	Dis- seminated (8 cases)		
Total leukocyte count (per cu.				
	10 000	13 400		
mm.)	10,900	13,400		
mm.) Segmented neutrophils (%)				
mm.)Segmented neutrophils (%) Lymphocytes (%)	69	66		
mm.)	69	66 28		
	69	66 28		

TABLE III
OBSERVATIONS IN FOURTH WEEK OF DISEASE

	Coccidioidomycosis			
Observation	Primary (42 cases) *	Dis- seminated (8 cases)		
Symptoms present	15%	28%		
Temperature elevation	2%	100%		
Weight loss	16%	84%		
Weight gain	16%	0		
Extrapulmonary physical find- ings	0	71%		
Leukocytosis (more than 10,000 per cu. mm.)	12%	43%		
Elevated erythrocyte sedimen- tation rate	71%	84%		
Hematocrit less than 40%	0	50%		

* Those with normal values during weeks 1 to 3 were not rechecked in week 4; those with abnormal findings were rechecked in week 4.

count was somewhat higher in the disseminated group.

Course in Hospital. Table III lists the findings upon re-evaluation in week 4. Temperature elevation, weight loss, extrapulmonary physical findings and anemia were common in the disseminated group. No remarkable differences were found regarding symptoms, leukocyte counts, or erythrocyte sedimentation rates. The site and time of the initial extrapulmonary spread are given in Table IV.

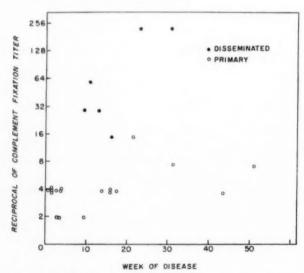


Fig. 2. Maximum complement fixation titers in twentyfour cases of coccidioidomycosis.

SITE AND TIME OF FIRST EXTRAPULMONARY SPREAD IN EIGHT
CASES OF DISSEMINATED COCCIDIOIDOMYCOSIS

Case No.	First Site of Dissemination	Week
111	Blood stream	1
IV	Supraclavicular node	2
v	Supraclavicular node	2
VI	Supraclavicular node	2
VII	Skin	2
VIII	Meninges	7
IX	Supraclavicular node	7
x	Peritoneal cavity	20

Maximum complement fixation titers clearly separated the two groups (Fig. 2), with one exception (Case II, vide seq.). Even though titers rose rapidly in the disseminated group, they did not reach the high levels usually associated with dissemination until long after extrapulmonary spread had occurred. (Table v.) The results of skin tests were usually positive as dissemination took place, then reverted to negative as humoral complement-fixing antibody titers rose.

Roentgenograms. Primary group: Table vi gives the progression of roentgenologic findings. The most common presenting finding was a pulmonary infiltrate in the lower lobe of the left lung (seventeen of forty-two patients). Infiltrates were accompanied by hilar adenopathy in 50 per cent of cases; both of these abnormalities disappeared gradually as evident on subsequent roentgenograms. Final roentgenograms showing granuloma formation were more common than not. A thick-walled cavity was intermittently present in one case. Paratracheal adenopathy was noted on admission in only one case. (Fig. 3.)

Table v
COCCIDIOIDIN SKIN TESTS AND COMPLEMENT FIXATION
ANTIBODIES DURING AND FOLLOWING
EXTRAPULMONARY SPREAD

	Duri	ing Disser	mination	Fo	llowing Dissem	ination
Case No.	Week	Skin Test	Comple- ment Fixation Titer	Week	Skin Test	Complement Fixation Titer
IV	2	3+	1:4		Not checked	
v	2 3 2 7	2+	1:4	15	1+	1:64
VI	3	2+	1:2	11	0	1:16
VII	2	3+	1:2	14	0	1:16
ıx	7	1+ (1:10)	1:32	12	0	1:128

TABLE VI
INITIAL AND FINAL CHEST ROENTGENOGRAMS IN
FORTY-TWO CASES OF PRIMARY PULMONARY
COCCUDIOLOGYCOSIS

No. of Patients	Initial	Approxi- mate Size (cm.)	Final	Approxi- mate Size (cm.)
24	Infiltrate	3.2	Granuloma	1.5
11	Infiltrate	3.3	Clear	
3	Effusion	***	Granuloma or clear	
2	Pleural reaction		Clear	
2	Normal		Normal	

Roentgenograms were taken serially (usually at weekly intervals) in all patients until either clearing of the initial lesion or granuloma formation occurred. Pleural reaction usually accompanied these findings. In thirty-two of the forty-two patients, roentgenograms showed that the condition of the chest became stable in four weeks or less. In three, infiltrates decreased in size by week 4, with equivocal granuloma formation. In three others, the findings remained unchanged at follow-up examinations (five to twenty-seven weeks).

In the remaining four patients, the roentgenograms showed slow clearing of the lesion. A massive pleural effusion in one patient slowly subsided by eight weeks. In two others, infiltrates cleared in eight to nine weeks. In one patient with infiltration of the lower lobe of the left lung transbronchial spread subsequently developed bilaterally, with hilar and paratracheal adenopathy (Case II). Resolution then occurred until only a faint density was present at week 12.

Disseminated group: Initial chest roentgenograms in six patients (Cases III to VI, IX and X)

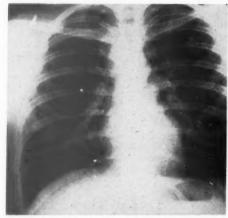


Fig. 3. Chest roentgenogram on admission in one patient with primary pulmonary coccidioidomycosis who showed paratracheal adenopathy.

were remarkably similar. (Fig. 4 and 5.) The most striking findings were right hilar and paratracheal adenopathy. Only one patient in the primary group had the latter finding. (Fig. 3.) The cardiomegaly seen in one patient (Case III) was caused by a diffuse coccidioidal myocarditis. Initial infiltrates were present in the right lung in five patients (lower lobe in three and upper lobe in two) and the left lung in two, (one in each lobe). The average size of infiltrate was 4.4 cm. Roentgenograms were taken at weekly intervals. In week 4, paratracheal adenopathy persisted in five of the six patients mentioned; one patient (Case III) died during week 1.

('Infiltrates cleared completely by week 4 in only one patient; bilateral transbronchial spread occurred in two patients in week 4, and in another in week 5. Slow clearing after week 4 was evident in all patients and was apparently altered by therapy. A thin-walled cavity (primary or acute cavity according to Winn's [3] classification) appeared transiently in one patient (Case VIII) in week 6. The earliest spon-



Fig. 4. Cases III, IV and V. Chest roentgenograms on admission.



Fig. 5. Cases vi, ix and x. Chest roentgenograms on admission.

taneous clearing occurred in week 14 (Case x). Individual roentgenograms are discussed in the case reports to follow.

ANALYSIS AND ILLUSTRATIVE CASE REPORTS

General Observations. The two groups of patients described were separated on the basis of complement fixation titers and evidence of extrapulmonary spread of C. immitis. The data indicate that careful attention to historic facts, laboratory and physical examinations, and clinical progression may give strong presumptive evidence of disseminated coccidiodomycosis soon after the initial infection. Tables VII and VIII sum-

Table vII

MAJOR DIFFERENCES FOUND BETWEEN THE TWO TYPES
OF COCCIDIOIDOMYCOSIS UPON ADMISSION TO
THE HOSPITAL

	Coccidio	domycosis	
Findings	Primary (42 cases)	Dis- seminated (8 cases)	
History			
Negro	12%	62%	
Chief complaint of chest pain	84%	25%	
Chief complaint of malaise,			
etc	4%	65%	
Duration of symptoms (days)	4	10	
Weight loss	5%	88%	
Physical examination			
P.M. temperature elevation			
(°F.)	100.3	102	
Chest splinting and/or rub	81%	12%	
Extrapulmonary findings	0	25%	
Laboratory			
Total leukocyte count (cu. mm.)	10,900	13,400	
(roentgenogram)	2%	75%	

marize major points of difference observed between primary pulmonary and disseminated coccidioidomycosis in this series of fifty patients. Because of the disparity in size of the two groups, they are most easily compared in terms of percentages. With only eight patients in the disseminated group, however, only gross differences in percentages should be accepted as meaningful.

It is evident that upon admission to the hospital one should be particularly suspicious of dissemination in Negro patients with a long (more than one week) history in which the chief complaints are of systemic rather than local nature, and in whom weight loss has occurred. Physical examination is not likely to be helpful unless presumptive evidence of extrapulmonary spread is present. A markedly elevated total leukocyte count or the presence of anemia is suspicious. A chest roentgenogram showing

Table viii

MAJOR DIFFERENCES FOUND BETWEEN THE TWO TYPES
OF COCCIDIODOMYCOSIS: WEEK 4 OBSERVATIONS

	Coccidioidomycosis			
Findings	Primary (42 cases)	Dis- seminated (7 cases)		
P.м. temperature elevation	2%	100%		
Extrapulmonary physical find- ings	0	71%		
Stable	78%	0		
Probably stable	14%	0		
Unstable	8%	100%		
Infiltrate	5%	71%		
Transbronchial spread	2%	29%		
Paratracheal adenopathy	2%	71%		

paratracheal adenopathy is unusual in primary pulmonary coccidioidomycosis, but it does occur.

A presumptive diagnosis of disseminated coccidioidomycosis can usually be made by careful re-evaluation of the patient in the fourth week of the disease. The chief complaint and weight loss may still persist. Afternoon temperature elevation in week 4 is suggested of extrapulmonary spread. Physical evidence of dissemination (supraclavicular adenopathy, septicemia, skin lesions) is often present and is probably the single most helpful finding early in the course of disseminated coccidioidomycosis. A change on chest roentgenograms is ominous. The usual findings are slowly clearing infiltrates, mediastinal (especially paratracheal) adenopathy and transbronchial spread.

A definite diagnosis of disseminated coccidiodomycosis depends ultimately upon demonstration of the organisms in an extrapulmonary site. Pathologic characteristics are helpful, but definitive diagnosis depends on culture and animal inoculation [2]. Biopsy material must be obtained from palpable lymph nodes or skin lesions. Blood cultures are taken, especially in fulminant cases. Spinal puncture is performed if headache or meningeal signs appear. Serologic titers are helpful, but diagnostic rises lag behind clinical suspicions of dissemination. Results of serial skin tests become positive just before or at the time of dissemination and then revert to negative as the complement fixation titers rise and dissemination progresses.

CASE REPORTS

To illustrate the point that accurate clinical differentiation between primary and disseminated coccidioidomycosis can usually be made, the following examples are cited. The case reports emphasize the criteria already discussed and summarized in Table VIII.

Case 1. Mild primary pulmonary coccidioidomycosis: This thirty-three year old white woman entered the hospital because of pleuritic type pain in the right anterior part of the chest, dry cough, malaise and fever, all of four days' duration. There had been no weight loss. The oral temperature was 100°F. Physical examination was within normal limits except for mild limitation of motion of the right hemithorax with inspiration. The total leukocyte count was 11,000 cells per cu. mm. with 3 per cent eosinophils. Chest roentgenogram revealed a fan-shaped area of pneumonia involving the upper lobe of the right lung. The patient was hospitalized for eight days. At the time of dis-

charge, chest pain had vanished, the temperature was normal and roentgenograms showed marked clearing. History, physical examination and roentgenograms in the fourth week were completely within normal limits. The coccidioidal complement fixation titer was 1:4 and the precipitin titer was 1:10.

Comment: Patients similar to this make up the majority of the primary pulmonary group. As already noted, forty of these forty-two patients were followed-up for longer than four weeks to rule out later dissemination.

CASE II. Severe primary pulmonary coccidioidomycosis: A thirty-seven year old white man entered the hospital because of pleuritic pain in the left side of the chest of four days' duration. He denied weight loss. The only positive physical findings were an oral temperature of 99°F. and rales in the lower lobe of the left lung. The total leukocyte count was 13,000 cells per cu. mm. with 81 per cent neutrophils and 19 per cent lymphocytes. Chest roentgenograms showed a patchy infiltrate in the lower lobe of the left lung and a blunting of the left costophrenic angle. During the first two weeks of hospitalization the patient was acutely ill. There was an unremitting non-productive cough, chills, sweats and substernal distress. The rales in the lower lobe of the left lung persisted. The total leukocyte count was 16,900 to 17,500 cells per cu. mm. with no change in the differential count except for the appearance of 5 per cent eosinophils. Roentgenograms showed a progressive increase in pneumonia in the lower lobe of the left lung and left hilar and paratracheal adenopathy.

Gradual improvement occurred and in the fourth week dry cough was the only symptom. A few inspiratory rales remained at the lower lobe of the left lung. Afternoon temperatures averaged 99.2°F. The patient had lost 17 pounds. The total leukocyte count was 13,200 cells per cu. mm. with 13 per cent eosinophils. A chest roentgenogram showed diffuse bilateral transbronchial spread and paratracheal adenopathy. Because of these disquieting findings in week 4, a left scalene node exploration was performed; pathologic and bacteriologic examinations were within normal limits. By week 6, symptoms and abnormal physical findings disappeared. A chest roentgenogram showed clearing by week 9, except for a small, fibrotic-appearing area in the lower lobe of the left lung. Followup examinations at weeks 12, 17 and 24 were within normal limits. The maximum coccidioidal complement fixation titer was 1:16 in weeks 17 and 24. Results of the weekly coccidioidin skin tests were all equivocal or negative except during week 3, when they were 4 plus at twenty-four hours and 1 plus at forty-eight hours.

Comment: This was an unusual form of primary pulmonary coccidioidomycosis in our series. The

complement fixation titer rose to high levels and the results of skin tests became negative after being positive in week 4. These findings suggest that the patient may have disseminated coccidioidomycosis, as yet unrecognized. Temperature elevation, rales, leukocytosis, and bilateral bronchogenous spread in week 4 also were suggestive of dissemination; however, no evidence of extrapulmonary spread has yet been found.

CASE III. Dissemination (septicemia): This twenty year old Negro woman entered the hospital because of a two-week history of fever, night sweats, chills, dyspnea, orthopnea and painful right ankle. A weight loss of 8 pounds had occurred prior to admission, Positive physical findings included a temperature of 104°F., pulse rate of 120, a palpable spleen and a warm, tender, swollen right ankle joint. The heart was enlarged to percussion. There were no murmurs. The total leukocyte count was 15,700 cells per cu. mm., with 24 per cent eosinophils; the hematocrit was 30 per cent, hemoglobin 8.9 gm. per cent. A chest roentgenogram (Fig. 4) showed cardiomegaly and marked hilar and paratracheal adenopathy.

The patient survived for only six days. Spiking fever, tachycardia and congestive heart failure increased despite therapy with massive doses of penicillin and streptomycin. Petechial hemorrhages appeared in the buccal mucosa. An urticarial rash was troublesome and unresponsive to treatment with antihistamines. Terminally, shock and hyperpyrexia were

unresponsive to corrective measures.

Five blood specimens taken on admission were subsequently positive for C. immitis on culture and mouse inoculation. Necropsy revealed extensive disseminated coccidioidomycosis, with marked involvement of the hilar and right paratracheal nodes. There was miliary pulmonary dissemination. Organisms resembling C. immitis were also found in the spleen, liver, gallbladder, appendix, retroperitoneal and intraabdominal lymph nodes, kidneys and bone marrow. There were no valvular heart lesions, but a diffuse granulomatous myocarditis was present. Culture of heart blood was positive for C. immitis.

Comment: This accelerated form of coccidioidomycosis is unusual, but illustrates the need for establishing clinical criteria upon which to make a presumptive diagnosis of dissemination. The marked right paratracheal adenopathy and eosinophilia on admission should have suggested disseminated coccidioidomycosis. It is possible that early amphotericin B treatment would have prevented the subsequent rapid deterioration.

Case IV. Dissemination (lymphadenopathy): A twentyeight year old Negro man entered the hospital after

fainting in the barracks. He gave a seven-day history of a 4 pound weight loss. Four days prior to admission a dry cough began and for one day there had been a sharp pain in the right anterior part of the chest with inspiration. The temperature was 101°F, and the physical findings were within normal limits except for a few rales in the lower lobe of the right lung. The total leukocyte count was 9,000 cells per cu. mm. with a normal differential count. A chest roentgenogram (Fig. 4) showed a diffuse infiltrate in the lower lobe of the right lung and moderate hilar and paratracheal adenopathy. During the first week of hospitalization a right supraclavicular lymph node was found; a biopsy specimen of a lymph node on day 7 was positive on microscopic examination and culture for organisms resembling C. immitis.

The patient continued to have a dry cough and mild substernal distress for the first three weeks of hospitalization. Daily temperatures averaged 99.6° to 100°F. Supraclavicular adenopathy became more marked and a few posterior cervical lymph nodes developed. The total leukocyte counts were 7,400 to 8,200 cells per cu. mm. Chest roentgenograms showed some clearing of the infiltrate in the lower lobe of the right lung, but an increase in right hilar adenopathy. The coccidioidomycosis complement fixation titer was

By week 4 mild malaise was the only symptom. An additional weight loss of 4 pounds had occurred. Supraclavicular and right posterior cervical adenopathy persisted. A chest roentgenogram showed a pleural reaction in the lower lobe of the right lung, moderate right hilar, and minimal right paratracheal adenopathy. Because of these positive findings and the lymph node biopsy, the patient was given a course of amphotericin B therapy.

1:4 in week 2.

Comment: Positive evidence of extrapulmonary spread was obtained early in this patient. Observation until week 4 revealed that moderate adenopathy (hilar, paratracheal and supraclavicular) was the major clue to active disease. In our series, supraclavicular adenopathy was the most useful initial indicator of dissemination; this case typifies the course also observed in Cases v and vi.

CASE VII. Dissemination (cutaneous spread): This thirty-two year old white man entered the hospital because of a diffuse parenchymal infiltrate throughout the upper and lower lobes of the left lung, first discovered on a routine roentgenogram taken for food handling purposes. Right scalene node biopsy specimen revealed a granuloma of unknown etiology; culture and animal inoculation revealed the organisms of Cryptococcus neoformans. The patient had been hospitalized four weeks for this diagnostic work-up when he suddenly began to have elevated tempera-

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tures (range 99° to 103°F.). There was associated malaise, nausea, anorexia and chilly sensations, but no chest pain. Physical examination remained within normal limits. The total leukocyte count, previously 4,100 to 7,500 cells per cu. mm. rose to 13,250 cells per cu. mm., with 79 per cent neutrophils, 17 per cent lymphocytes, 4 per cent eosinophils. A chest roentgenogram showed that the infiltrates in the left lung were unchanged, but a new diffuse infiltrate involving the lower lobe of the right lung had appeared. Symptoms gradually subsided after one week; fever lasted ten days. Seven days after the onset of fever a small furuncular lesion appeared over the left scapula. During the next two weeks this lesion expanded until it was about 3 cm. in diameter with a surrounding halo of 19 cm. The total leukocyte count was unchanged. During weeks 2 and 3 after onset of fever the chest roentgenograms showed gradual increase in the infiltrate in the lower lobe of the right lung, and then clearing. There was associated mild right hilar adenopathy. In week 4 no new physical findings had appeared. The total leukocyte count was 6,300 cells per cu. mm. with 26 per cent eosinophils. The infiltrates in the chest were unchanged.

The diagnostic problem was solved in week 5 when a skin aspiration from the lesion was positive microscopically for spherules resembling C. immitis; subsequent culture and mouse inoculation supported this impression. Skin biopsy reconfirmed the diagnosis. During weeks 6 to 9 the only positive findings were the slowly growing skin lesion and the appearance of a small nodule on the upper left part of the lip which was not biopsied. The coccidioidomycosis complement fixation titer was 1:4 and the precipitin 1:10 in week 3. Chest roentgenograms showed gradual clearing of the infiltrates in the lower lobe of the right lung; a roentgenogram in week 9 showed no change from that obtained on admission (infiltrates on the left presumably due to pulmonary cryptococcosis). A course of amphotericin B therapy was then started.

Comment: This was an unusual case and the only one we had under observation before, during and after coccidioidal infection. While being investigated for pulmonary cryptococcosis, disseminated coccidioidomycosis developed (presumably from exposure to dust on the hospital grounds). The first evidence of dissemination was an extrapulmonary lesion, at first insignificant in appearance, but indolent and progressive. A chest roentgenogram showing slow clearing of the lesion, without paratracheal adenopathy, was the only other finding suggestive of dissemination in week 4.

Case viii. Dissemination (meningitis): This twenty-one year old Negro man entered the hospital with a twenty-one day history of malaise and night sweats.

Two days before admission he noted a mild substernal pain which increased with deep inspiration. Physical findings on admission were within normal limits except for a temperature of 99°F. and some limitation of diaphragmatic excursion bilaterally upon inspiration. The total leukocyte count was 7,900 cells per cu. mm., with a normal differential count. The reaction of skin tests to coccidioidin 1:100 were negative on admission and positive by week 3. For the first four weeks of hospitalization the patient had an irregular fever with temperatures averaging 99.6°F; associated with this was a 4 pound weight loss and continued malaise. Chest roentgenograms on admission showed a hazy pneumonitis in the lower lobe of the left lung; weekly roentgenograms disclosed gradual development of a thin-walled cavity as the diffuse infiltrate became more mottled and contracted. Hilar and paratracheal adenopathy appeared.

Because of the persistent fever and delayed clearing as seen on the chest roentgenogram by week 4 a left scalene node biopsy was performed. There were no pathogenic organisms. During weeks 5 and 6 the temperature returned to normal and the roentgenogram showed improvement until the cavity was only 1.5 cm. in diameter. He was discharged at the end of six weeks to return to light duty.

One week after discharge he began having severe headaches and was readmitted for observation. Lumbar puncture revealed organisms resembling C. immitis on direct examination; subsequent cultures and animal inoculations confirmed the diagnosis of coccidioidal meningitis.

Comment: This case illustrates the occasional difficulty of making an early diagnosis of disseminated coccidioidomycosis. Because of persistent fever and slow clearing as seen on the roentgenograms, and despite cavitary disease, dissemination was suspected in week 4 and a scalene node biopsy was performed; unfortunately, this was within normal limits. Had amphotericin B therapy been started because of the suspicious week 4 findings, meningitis might have been prevented.

Case x. Dissemination (peritonitis): This twenty-six year old Negro man entered the hospital with chief complaints of malaise and weight loss of 10 pounds for two weeks prior to admission. Physical examination was within normal limits except for a temperature of 101.4°F. and rales at the base of the right lung. The total leukocyte count was 9,200 cells per cu. mm. with a normal differential count; the hematocrit was 45 per cent. A chest roentgenogram (Fig. 5) revealed a diffuse infiltrate in the lower lobe of the right lung, moderate hilar adenopathy and minimal right paratracheal adenopathy. Malaise, temperature elevation (99° to 101°F.) and rales persisted during weeks 2 and

3. The infiltrate cleared slightly, but adenopathy persisted.

In week 4 the temperature averaged 99.8°F. Easy fatigability was the only complaint. The total leukocyte count was 6,200 cells per cu. mm. and a chest roentgenogram showed no changes. There was slow clinical improvement between weeks 5 and 10, as the patient was allowed out intermittently on pass. A roentgenogram showed only hilar adenopathy in week 8, but in week 10 there was sudden appearance of a new infiltrate in the upper lobe of the right lung. The hematocrit had dropped to 34 per cent. The infiltrate cleared by week 12 and the patient was returned to light duty.

He returned voluntarily to the hospital in week 20 because of a right inguinal hernia. Physical examination and laboratory values (including chest roentgenogram and hematocrit) were otherwise within normal limits. At surgery, the hernia sac was studded with granulomatous lesions; subsequent laparotomy revealed 2 L. of ascitic fluid and implants scattered over the peritoneum, small bowel, cecum and ascending colon. A biopsy specimen revealed a non-specific granulomatous reaction; cultures for fungi were not taken, but routine cultures were negative. In week 23 the coccidioidal complement fixation was at least 1:32 (highest dilution checked). Because of his good condition at that time no therapy was administered.

The patient was rehospitalized for complete evaluation in week 85. He had had no specific complaints. Physical examination was within normal limits except for small posterior cervical lymphadenopathy and vague abdominal tenderness. A biopsy specimen of a small cervical node was within normal limits. The coccidioidomycosis complement fixation titer was 1:256. A chest roentgenogram was within normal limits. Follow-up examination at weeks 86, 107 and

129 revealed no abnormalities.

Comment: This patient was the first in our series. Although dissemination was not feared until week 20 when peritonitis was found, in retrospect it should have been suspected earlier. The temperature elevation and hilar adenopathy in week 4 were suggestive; the appearance of anemia and right apical infiltrate in week 10 should have prompted a careful search for extrapulmonary spread. Fortunately, his untreated course has been favorable to date.

THERAPY

Primary Coccidioidomycosis. All patients were treated with bed rest and symptomatic care during the acute phase of the disease. Gradual ambulation was permitted in the first week of hospitalization in most cases. Twelve patients

received penicillin; four, broad-spectrum antibiotics; and twenty-six, no therapy. No difference was seen in the rate of recovery between treated and untreated patients. Patients were returned to duty when the roentgenograms were clear or showed granuloma formation. In the majority of cases this was accompanied by normal physical findings and laboratory values. Erythrocyte sedimentation rates, however, were still elevated in thirty of forty-two patients when they were discharged from the hospital. Repeat examinations at intervals greater than six weeks were made in nineteen. In none of these was there laboratory or physical evidence of dissemination. Four continued to have elevated erythrocyte sedimentation rates. Follow-up observations in nine of the twelve patients discharged with normal erythrocyte sedimentation rates also revealed no evidence of dissemination.

Disseminated Coccidioidomycosis. Patients in this group also were allowed to ambulate as soon as the acute phase of the disease had subsided. Two patients (Cases VIII and x) were returned to duty before dissemination became apparent. In four patients a variety of agents, including penicillin, broad-spectrum antibiotics, ACTH, Captan* (a plant fungicide) and griseofulvin were without

effect.

Amphotericin B was administered to six of the eight patients. The results of therapy in two (Cases v and vi) are shown in Figures 6 and 7. Because no amphotericin B was given to one (Case v) for the first twenty-seven weeks of hospitalization, he serves as a control against whom therapy in the other (Case vi) may be compared. The temperature and total leukocyte counts rapidly returned to normal in both patients, with or without therapy. Chest roentgenograms taken during weeks 1 (Fig. 4 and 5, Cases v and vi) and 5 were comparable, but rapid clearing (by week 10) in one patient (Case vi) occurred with therapy, while persistent adenopathy in weeks 9 and 27 was noted in the other (Case v). (Fig. 8 and 9.) In both patients coccidioidal complement fixation titers returned to low levels only following therapy. The most distressing feature in Case v was the inexorable progression of physical findings before treatment. The increasing supraclavicular adenopathy in Case vi faded rapidly with therapy and no new lesions appeared. Belated therapy in Case v

^{*} N-trichlormethylmercapto-4-cyclohexane-1,2 dicarboximide, Stauffer Chemical Co., Chauncey, New York.

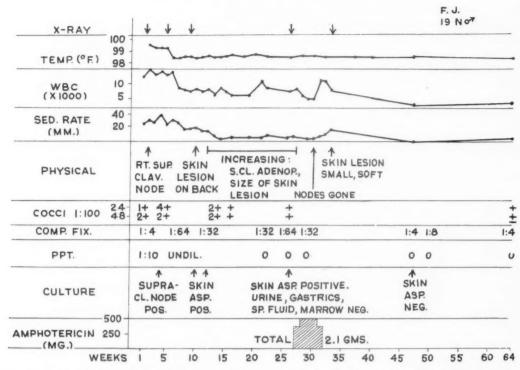


Fig. 6. Case v. Clinical course of patient with disseminated coccidioidomycosis with spread to supraclavicular nodes and skin.

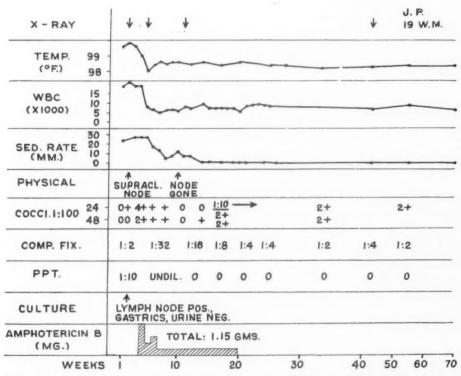


Fig. 7. Case vi. Clinical course of patient with disseminated coccidioidomycosis with lymphogenous spread.



Fig. 8. Case v. Chest roentgenograms obtained during weeks 5, 9 and 27. Note gradual clearing without therapy.



Fig. 9. Case vi. Chest roentgenograms obtained during weeks 5, 10 and 43. Note rapid clearing by week 10 with amphotericin B therapy.

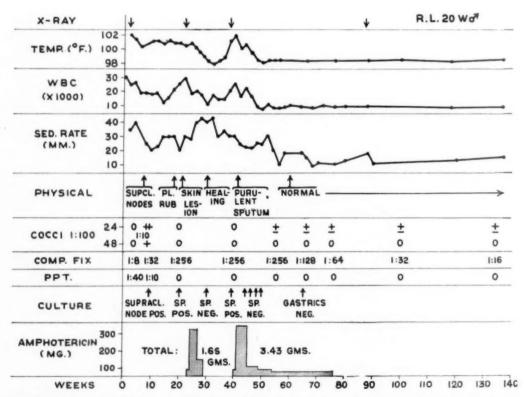


Fig. 10. Case ix. Clinical course of patient with disseminated coccidioidomycosis with supraclavicular adenopathy, purulent bronchitis and cutaneous spread.



Fig. 11. Case IX. Chest roentgenograms obtained during weeks 22, 38 and 87. Note that complete clearing occurred only after the second course of amphotericin B therapy.

(cut short by the patient's disappearance from the hospital) was followed by disappearance of adenopathy and softening of the skin lesions as the complement fixation titer fell. No further evidence of dissemination was seen in either patient at subsequent examinations.

Case IX was the subject of a previous report [16]. Figure 10 summarizes the patient's clinical course. A temporary remission manifested by a fall in temperature and in total leukocytes and conversion of the sputum to negative, occurred after the first course of amphotericin B (total dose 1.66 gm. in the period from week 23 to week 29). Eleven weeks later, however, an exacerbation occurred as the temperature and total leukocyte count rose, a chest roentgenogram showed worsening (Fig. 11), and a great quantity of purulent sputum loaded with C.

immitis was produced. A second course of amphotericin B (3.43 gm. from weeks 40 to 76) was administered with good results. Follow-up examination sixty-four weeks later revealed no evidence of disease.

The results of therapy in all five patients treated with amphotericin B are summarized in Table IX. The two patients with lymphogenous spread (Cases IV and VI) recognized and treated early in the course of the disease, required the least medication. Two others with early lymphogenous spread (Cases V and IX) were treated late in the course of the disease and required larger doses and longer duration of therapy. The skin lesion in one (Case VII) was slow to heal and this patient required the largest total dosage. Follow-up examinations revealed no progression of clinical, roentgenologic or serologic findings.

TABLE IX
RESULTS OF AMPHOTERICIN B THERAPY IN FIVE CASES OF DISSEMINATED COCCIDIOIDOMYCOSIS

Case	Amphotericin B	Doses	Weeks		lement ation	Ches Roentgene	-	Follow-up	D. Iv.	
No.	(gm.)	(no.)	(no.)	Before Therapy	After Therapy	Before Therapy	After Therapy	(weeks after therapy)	Results	
IV	1.83	25	18	1:4*	0	Paratracheal adenopathy	Negative	17	Excellent	
v	2.10	35	5	1:64	1:4	Negative	Negative	32	Good	
VI	1.15	24	16	1:2*	1:2	Paratracheal adenopathy	Negative	50	Excellent	
VII	6.39	56	19	1:4†	1:2	Infiltrate in lower lobe of right lung	Clearing	32	Good	
IX	5.09	90	41	1:256	1:16	Paratracheal adenopathy	Negative	64	Excellent	

^{*} Complement fixation rise to 1:32 after therapy started.

[†] Complement fixation rise to 1:16 after therapy started.

TABLE X

Case No.		lood Ur Nitroge (mg. %	n	Urine Concentrating Ability (specific gravity)				Casts			olsulfonph Excretion 15 minute	n
	(1)	(2)	(3)	(1)	(2)	(3)	(1)	(2)	(3)	(1)	(2)	(3)
IV	12	27	15	1.022	1.026		0	Hyaline	0		25%	
v	10	29	20	1.026	1.015	1.025	0	Granular	0	25%	10%	
VI	16	20	14	1.028	1.029	1.027	0	Hyaline, granular	0	35%	35%	40%
VII	13	46	18	1.022	1.015		0	Hyaline, granular	0	35%	5%	40%
IX	11	50	22	1.024	1.015	1.027	0	Hyaline, granular	0	35 %		

* (1) Before therapy.

(2) During therapy.

(3) After therapy.

† Two-hour phenolsulfonphthalein excretion.

Two untreated patients (Cases III and x) had markedly different courses. As already indicated, coccidioidal septicemia caused death in one (Case III), while coccidioidal peritonitis did not interfere with subsequent apparent good health in the other (Case x). The final patient (Case VIII) has recently received amphotericin B intravenously and intrathecally for coccidioidal meningitis.

Negligible toxicity of the drug was noted. Reversible renal abnormalities were the major side effects seen. (Table x.) There was no evidence of hepatic toxicity or bone marrow suppression except for a transient anemia in one case (Case VII) which paralleled the blood urea nitrogen rise. Chills, fever, anorexia and malaise during and following infusions occurred in all patients at variable times, but were most prominent with earlier infusions.

COMMENTS

It has been said that coccidioidomycosis is "a disease without a natural history" [6]. The present study refutes this statement. Primary pulmonary coccidioidomycosis follows a typical course and can usually be differentiated from disseminated coccidioidomycosis within one month from the onset of disease. Initial extrapulmonary spread occurs early in the course of the disease (before week 20 in all eight cases of this series). It is usually readily apparent on physical examination. Early clues are available

from the history, laboratory results and roentgenograms. This concept of the progression of disseminated coccidioidomycosis from the initial primary infection has become widely accepted and has prompted Smith [7] to term the disease "progressive primary coccidioidomycosis."

Three other studies in which patients were followed-up from the onset of the disease have shown the importance of this concept [8–10]. In these, a total of ten cases of disseminated coccidioidomycosis were studied. Dissemination to skin, lymph nodes, meninges or blood stream occurred between weeks 1 and 10 in seven patients. In one patient there was spread to bone in week 43. The time of dissemination was not given in the other two patients. Persistently elevated total neutrophils and temperature, and slow clearing, as seen on roentgenograms, with marked mediastinal adenopathy were characteristic of all patients.

Nevertheless, confusion still exists concerning late "progression" or "dissemination" of coccidioidomycosis. Smith [7] has stated that late dissemination may occur, but it is rare and more often represents an exacerbation of a quiescent infection which has previously disseminated. Small [11] has recently reported four cases of late "progression" of pulmonary coccidioidomycosis in which the best documented case implies bronchogenic "dissemination" from a coccidioidal cavity one month after the cavity was first discovered. Our experience supports Smith's

concept of the natural history of the disseminated disease. All eight cases of extrapulmonary spread occurred within twenty weeks and seven within seven weeks of the pulmonary infection. No evidence of progression was noted in forty-two cases of primary pulmonary coccidioidomycosis followed for periods up to one year from the initial infection. No prolonged follow-up examinations were performed in the disseminated group to study further progression of disease. Thus late "progression" of previously disseminated cases was not ruled out; however, initial dissemination always occurred early in the course of the disease in our patients.

In the disseminated group, the reaction to coccidioidin 1:100 skin tests typically became positive at the time of the first obvious extrapulmonary spread. In the patients followed-up with serial skin tests a subsequent reversion to a negative reaction occurred after the complement fixation titers rose and dissemination progressed. Thus delayed hypersensitivity preceded circulating antibody formation; however, as circulating antibody titers rose, delayed hypersensitivity often disappeared. This is in accord with recent experiments [13] in which injection of large amounts of antigen suppressed delayed hypersensitivity and caused increases in circulating antibody. Although no serial skin tests were made in the primary group, the experience of others [14] has demonstrated that reversion of the coccidioidin skin test reaction to negative in non-progressive coccidioidomycosis is rare. A change from a positive to a negative skin test reaction is of ominous significance, but is often of little help because it occurs long after dissemination has become clinically manifest.

It is not the principal purpose of this paper to evaluate therapy of coccidioidomycosis. Certain statements, however, should be made. The policy at Davis-Monthan Air Force Base has been to ambulate patients with coccidioidomycosis early in the course of the disease [12] and the results in the primary group would appear to support this policy. However, two of eight patients with disseminated coccidioidomycosis were returned to duty before extrapulmonary spread was recognized. Undue leniency must therefore be avoided. An elevated erythrocyte sedimentation rate does not constitute a contraindication to discharge from the hospital. Such patients, however, should be followed up until it is normal. The therapy of disseminated coccidioidomycosis has recently been reviewed [15-18], with conflicting results regarding amphotericin B. Many treatment failures reported by others are accounted for by advanced disease, insufficient amount of the drug administered or inadequate duration of treatment [79]. Recent results are more favorable [20].

Our data indicate that amphotericin B is an effective agent. The daily dosage should be 1 to 1.5 mg. per kg. intravenously, diluted in 500 to 1,000 cc. of 5 per cent dextrose in water and administered for four to six hours. Small doses are used every other day for the first week until the maximal dosage, short of undue renal injury (best estimated by weekly urinalyses and blood urea nitrogen determinations) is achieved. If tolerated, this amount is given every forty-eight to seventy-two hours until cultures, total leukocyte count, chest roentgenogram, erythrocyte sedimentation rate, weight and temperature are normal, and the coccidioidal complement fixation titer has fallen to a low value (preferably 1:4 or below). In the last month or two of therapy infusions may be given once weekly if the course is favorable. Chills, fever and anorexia are common side effects, particularly in the first few weeks of therapy, and can be partially controlled with the administration of 0.6 to 1 gm. of acetylsalicylic acid and 25 mg. of chlorpromazine orally. Rotating vein sites minimizes the danger of phlebitis.

If treatment is started early in the course of lymphogenous spread (as in Cases IV and VI herein cited), remission may be expected with a total dosage of 1 to 2 gm. given for about four months. Patients with skin lesions and coccidioidal meningitis require larger total doses and more prolonged therapy. Intrathecal administration may be necessary [20]. Those treated late in the course of the disease, perhaps long after early lymphogenous spread (as in Cases v and ix), require the largest doses of amphotericin B. Patients in this group should usually receive from 4 to 6 gm. for eight to twelve months after treatment is started. It is reasonable, in the present state of our knowledge, to recommend that amphotericin B therapy be started as soon as the diagnosis of disseminated coccidioidomycosis is made.

SUMMARY

Fifty cases of coccidioidomycosis were first observed shortly after the onset of the disease and followed-up for as long as three years thereafter. The clinical course in forty-two patients with

primary pulmonary coccidioidomycosis was compared with that of eight patients with disseminated coccidioidomycosis. It was found that certain characteristics clearly separated the two groups. (1) Soon after the primary infection, dissemination (extrapulmonary spread) could be suspected in patients with a history of weight loss, prolonged duration of generalized symptoms and chest roentgenograms showing paratracheal adenopathy. (2) Four weeks after the initial infection a presumptive diagnosis of disseminated coccidioidomycosis could be made on the basis of persistent temperature elevations, physical evidence of extrapulmonary spread (adenopathy, skin lesions, meningeal signs) and slow clearing as seen on chest roentgenograms. (3) Skin test anergy usually appeared as serum complement fixation titers rose to a disseminated range, but lagged behind those clinical signs which indicated extrapulmonary spread. (4) Dissemination occurred within seven weeks of the primary infection in seven patients and was first recognized in week 20 in the eighth. (5) Diagnosis of disseminated disease was confirmed by isolation of C. immitis from an extrapulmonary site or maximum coccidioidal complement fixation titer of 1:32 or greater.

Early ambulation and return to duty failed to have an adverse effect on forty-two patients with primary pulmonary coccidioidomycosis. An elevated erythrocyte sedimentation rate was not regarded as a contraindication to discharge. All patients healed without receiving amphotericin B therapy and evidence of dissemination was not seen in any patient for as long as fifty-two weeks.

Amphotericin B was an effective agent in the therapy of disseminated coccidioidomycosis. Five patients received a total intravenous dosage of 1.15 to 6.39 gm. for five to forty-one weeks. All exhibited a fall in coccidioidal complement fixation titer and disappearance of physical and roentgenologic evidence of disease. Evidence of exacerbation was not encountered up to sixtyfour weeks after infusions were stopped. Response in a patient with lymphogenous dissemination was clearly better than in an untreated control patient. Reversible renal abnormalities were the major manifestations of amphotericin B toxicity in all patients, but this did not preclude its use.

It is recommended that amphotericin B therapy be started as soon as a diagnosis of extrapulmonary spread from primary pulmonary coccidioidomycosis is made. A total dosage of 1

to 2 gm. over a period of four months is usually adequate for patients treated soon after the original lymphogenous spread. Those treated later in the course of the disseminated disease require from 4 to 6 gm. for eight to twelve months after treatment is started. In all patients with disseminated disease, therapy is given in divided doses until cultures, total leukocyte count, chest roentgenogram, erythrocyte sedimentation rate, weight and temperature are normal, and the coccidioidal complement fixation titer has fallen to a low value (1:4 or below).

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Cavitary Histoplasmosis Complicated by Fungus Ball*

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ASPERGILLOSIS of the lung has been known for many years [24,34], especially in France where numerous cases have been observed and reports published [7,26]. In this country, aspergillus infection of the lung has been found in increasing frequency in autopsy material and occasionally in surgical specimens [8,11,28,37]. Although "primary" aspergillosis has been described [1,4,15,18,32,36], the rarity of this entity and its relation to other debilitating diseases places it beyond the scope of this paper.

Solitary pulmonary nodules have been observed for many years. However, prior to the widespread use of photofluorograms and mass x-ray surveys these were seen relatively infrequently. The presence of such lesions in autopsy material also was rare. In the period since World War II there has been a tremendous increase in resection of such lesions because of suspected lung cancer. A significant percentage of these resected lesions turned out to be granulomatous rather than neoplastic. A large pathologic material of granulomatous solitary pulmonary nodules therefore has accumulated.

When these lesions were first recognized they were called tuberculoma because, despite difficulty in demonstration of etiologic agents, tuberculosis was considered the invariable cause of such lesions. With the advent of special stains and particularly with greater understanding of the frequency of fungus infections, the true nature of these lesions has been elucidated. Although tuberculomas do of course occur, they are at present, in the respective endemic areas, less frequently seen than histoplasmomas, coccidioidomas and other non-tuberculous granulomas.

With greater understanding of the varied

etiology of such lesions has come recognition of a particularly interesting one. This is a circumscribed lesion made up of a cavity (of various etiology) filled by a mat of mycelium most frequently of species of aspergillus. These so-called aspergillomas may temporarily be indistinguishable from the other solitary pulmonary nodules mentioned. However, certain x-ray signs, particularly the appearance of a crescent-shaped shadow of air between the intracavitary inclusion and the wall of the cavity and the movements of the cavity contents on fluoroscopy have made the preoperative diagnosis of such lesions possible. The etiology of the cavities could not always be clearly established and they are frequently referred to as bronchiectatic.

The purpose of the present paper is to review over fifty cases of so-called aspergilloma and to describe four cases of cavitary histoplasmosis associated and complicated by aspergillosis within the histoplasmic cavity. (Table 1.)

MATERIAL AND METHODS

A total of fifty-eight cases, including the seven cases we have seen (the four cases reported in detail and three others of unknown cause noted in Table 1), make up the review from which the following clinical findings were noted. Of the fifty-eight cases, thirty of the fungus balls were found in the upper lobe of the right lung, twenty-three in the upper lobe of the left lung and only two in the middle lobe of the right lung and two in the lower lobes;† in both instances these latter two were in the apical segments of the lower lobes. Hemoptysis was a symptom in twenty-six cases (45 per cent). The cause of the cavity was known or suspected to be bronchiectasis in twenty-one cases. Tuberculosis was suspected as the cause in eleven cases, malignancy in two cases and histo-

† In three instances the lobes were not specified and two patients had cavities in two lobes.

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TABLE I FIFTY-EIGHT CASES OF "FUNGUS BALL"

Author	Case No.	Age (yr.), Race and Sex	Location of Fungus Ball	Fungus	How Identified	Cause of Cavity	Outcome
Schwarz, Baum	3	45,W,M 47,W,M 49,W,M	L.U.L. (hemoptysis)	Aspergillus Aspergillus Aspergillus	Histology Histology Histology	Histoplasmosis Histoplasmosis Histoplasmosis	Died R,L Died
Barlow [2]	4	70,W,M 25,F	L.U.L. L.U.L.	Unknown Aspergillus	Culture of	Histoplasmosis Tuberculosis, bronchiectasis	R,L
Bruce [3]	1	52,M 50,W,M	R.U.L. (hemoptysis) R.U.L. (hemoptysis)	Aspergillus A. fumigatus	empyema Histology Culture	Unknown Salmonella choleraesuis abscess	R,L R,L
DeMinjer [6]	1 2	21,M 59,M	R.U.L. R.U.L.	Aspergillus ?	Histology	with bronchiectasis Cavity possibly tuberculosis	R,L
Enjalbert et al. [7]	1 2	44,W,F 19,W,F	R.U.L. (hemoptysis) L.U.L. (hemoptysis)	Aspergillus ? Aspergillus	Histology Histology	Cavity possibly tuberculosis Cavity possibly tuberculosis Bronchiectasis? (present 10 years)	R,L R,L
Finegold et al. [8]	1 4	74,W,M 78,W,M	Both upper lobes	Aspergillus Aspergillus Aspergillus	Histology Histology Histology	Tuberculosis Non-specific pneumonia Non-specific pneumonia with ab- scess, possible staphylococcal infection (postoperatively)	R,L Died Died
	6	58,W,M 58,W,M	Left lung R.U.L. (multiple)	Aspergillus A. fumigatus	Histology Culture	infection (postoperatively) Carcinoma with abscess Hodgkin's disease after therapy for pneumonia	Died Died
	8	68,W,M	L.U.L.	A. fumigatus	Culture	Severe necrotizing staphylococcal (?) pneumonia	R,D
Fingerland et al. [9]	1 2 3	51,W,M 31,W,F 25,W,F	R.L.L. apex R.U.L. (hemoptysis)	Aspergillus Aspergillus Aspergillus	Histology Histology Histology	Bronchiectasis Postpneumonic abscess Healed tuberculosis; bronchiectasis	R,L R,L R,L
	5 6	35,W,F 47,W,F 53,W,F	L.U.L. L.U.L. L.U.L. (massive hemop- tysis)	Aspergillus Aspergillus Aspergillus	Histology Histology Histology	Tuberculosis Bronchiectasis Bronchiectasis	R,L R,L R,L
	7 8	45,W,M 55,W,F	L.U.L R.U.L.	Aspergillus Aspergillus	Histology	Bronchiectasis	R,D
Foushee, Norris [10]	1	44,M	R.U.L.	A. fumigatus	Histology Culture	Bronchiectasis Unknown, granulomatous	R,L R,L
Gerstl et al. [12]	1	55,N,F 33,F	R.U.L. (hemoptysis) L.U.L. (hemoptysis)	Aspergillus Aspergillus	Culture Histology	Possibly tuberculosis Bronchiectatic cyst	R,L R,L
Foushee, Norris [10] Friedman et al. [11] Gerstl et al. [12] Godfrey [13] Graves, Millman [14]	2	52,M 72,W,M	R.U.L. (hemoptysis) R.U.L.	Not identified Aspergillus or	Histology	Unknown Abscess, etiology unknown	R,L R,L
Hausman [16]	1	52,F	Apicoposterior segment	candida Aspergillus	Culture of	Bronchiectasis (?)	R,L
Hamphill [17]	1	55,M	R.U.L.	Aspergillus	Cavity Histology	Granulomatous with eosinophils, etiology unknown	Dr.,L
Hiddlestone et al. [19]	2 3	28,M 30,M	R.U.L. R.M.L.	A. fumigatus	Culture	Bronchiectasis	R,L
Hinson et al. [20]	2	58,M	Apical segment	A. fumigatus A. fumigatus	Culture Culture of sputum	Bronchial cyst or bronchiectasis Bronchiectasis	R,L R,L
Hochberg et al. [21] Hughes et al. [22]	3 4 1 1	57,M 50,F 48,W,M 56,N,M	R.U.L. (hemoptysis) R.U.L. (hemoptysis) L.U.L. (hemoptysis) L.U.L. (hemoptysis)	Aspergillus ? Not named Aspergillus	Histology Histology Culture and	Bronchiectasis Unknown, granulomatous Unknown, bronchiectasis? Bronchiectasis?	R,L Died R,L R,L
Levin [24]	1 2	82,M 38,M	R.U.L. (hemoptysis)	Candida (?) Unidentified	histology Histology Histology	Unknown Unknown	Died R,L
	3	25.M	R.U.L. (hemoptysis) R.U.L. (hemoptysis) R.U.L.	Unidentified Aspergillus	Histology Histology	Unknown Bronchiectasis	R,L R,L
Metras, Thomas [25]	1 1	60,M 40,M 42,M	R III.	Aspergillus	Histology	Probable tuberculosis	R,D
ccora, 1011 [27]		61,M	L.U.L. R.U.L., R.M.L.	Aspergillus Aspergillus	Histology Histology and	Tuberculosis Tuberculosis	R,D R,L
	3	39,M	(hemoptysis) L.U.L. (hemoptysis)	Aspergillus	Culture Histology and	Tuberculosis	R,L
Pesle, Monad [28]	2	33,F 42,M	R.U.L. (hemoptysis) L.U.L. (hemoptysis)	Not named Not named	culture	Unknown Lung cyst, possibly tuberculosis	R,D Dr.,L
Pimental [29]	3 4	35,M	L.U.L. (hemoptysis) Cavities not localized	Aspergillus Aspergillus	Culture Culture and	Bronchiectasis Unknown	R,L Unknown
rocknow, Loewen [30]	1 1	28,W,M 57,M	R.U.L. (hemoptysis) R.U.L. (hemoptysis)	Aspergillus A. fumigatus	histology Culture Culture from bronchial	Histoplasmosis Bronchiectasis (?) Granulomatous (?)	R,L L
Vellios et al. [34] Veens, Thompson [35]	1 2			Aspergillus None given (hyphae	aspirate Culture Histology	Bronchiectasis Smooth walled cyst, etiology un- known	R,L R,L
esner, Hurwitz [37]	1	35,W,M	Superior segment L.U.L.	only) A. fumigatus	Culture		R,L
chwarz, Baum	5 6 7	34,N,M	R.U.L.	fresenius Mucorales Aspergillus A. fumigatus	Histology Histology Culture	known Trauma Bronchiectasis Bronchiectasis	R,L R,L R,L

^{*}R.U.L., right upper lobe; L.U.L., left upper lobe; R.M.L., right middle lobe; R.L.L., right lower lobe.
†R,L, resection of lesion with recovery at last follow-up; L, living at last follow-up; R,D, resection of lesion but died; Dr.,L, cavity drained; patient living and well at last follow-up.
‡Following report by Levin [24]. Patient seen and resected with pathologic examination at Jewish Hospital, Cincinnati, Ohio.



Fig. 1. Case 6 (Table 1). Large apical cavity with fragments of fungus ball (arrow). Dilated bronchus leading into cavity.

plasmosis was known or suspected as the cause of the cavity in five cases. In forty-eight cases aspergillus was the fungus producing the fungus ball; twentyseven of these were diagnosed by histology alone, while twenty-one were proved by culture. Only one case of candida and one case of mucorales were noted in this series. The age range in this group of cases was from nineteen to eighty-two years, most of the cases (seventeen) occurring in the fifty-one to sixty year age group. There were forty-two men, fifteen women, and one case in which the sex was not noted. In twentyeight cases no mention was made of the race, but in the thirty in which this was mentioned twenty-seven were white and three were Negro. In forty cases the lesion was resected and the patients were living when last heard from; three were drained rather than resected but recovered from the surgery without complications. Thirteen of the fifty-eight patients were dead at the time reported. No attempt has been made to correlate the extent of the disease in the lungs with mortality since a large number of these patients had associated pulmonary insufficiency or were incompletely described.

RESULTS

It is safe to say that in the majority of the cases reported the origin of the cavities was assumed to be bronchiectatic and that the aspergillus found the environment of the bronchiectatic cavity favorable to its rapid development. (Fig. 1.)

The following case reports are unique in that the etiology of the cavity lesions was established

TABLE II

CONFIRMATIVE RESULTS OF DIAGNOSTIC LABORATORY
PROCEDURES IN FOUR CASES OF CAVITARY HISTOPLASMOSIS
COMPLICATED BY FUNGUS BALL

Case No.	Histo- plasma Capsu- latum Demon- strated	Highest Complement Fixation Titer for Histoplasmin	Aspergillus Species Demonstrated in Cavity
1 2	*	Not done 512 YP	# #*
2 3	#	512 YP	#
4	*	2048 YP	No anatomic material available

Note: * positive culture; # microscopic demonstration in tissue section; — negative; YP yeast phase antigen.

with certainty as histoplasmic. The presence of aspergillus in the lumen of the cavities caused special diagnostic problems. (Table II.)

CASE REPORTS

CASE 1. This forty-five year old white man was first hospitalized in 1941 because of "tuberculosis." The basis for this diagnosis is unknown. From that time until 1952 he was hospitalized repeatedly, the diagnosis of tuberculosis again being made without bacteriologic proof. In 1952 he was hospitalized and his sputum was positive on one occasion for acidfast bacilli. In August 1954, during hospitalization, multiple sputum examinations for acid-fast bacilli were negative, but roentgenograms showed extensive inflammatory changes bilaterally. At this time the patient was overtly psychotic and from then until his death spent most of his life in a state mental hospital. Physical examination revealed normal vital signs but marked emaciation and evidence of emphysema. Roentgenograms showed bilateral infiltrate in the upper lobes with cavitation. In one of the cavities a mass was seen with a crescent air meniscus above it, and the diagnosis of fungus ball was suspected. During hospitalization in November and December 1957 a sputum specimen was culturally positive for Histoplasma capsulatum. The patient's course was one of gradual deterioration and he died on December 16, 1957, apparently of cachexia and malnutrition.

At necropsy the left lung was covered by massive adhesions, which in many parts measured up to 4 mm. The upper lobe showed two cavities which were located approximately 4 cm. below the anatomic apex. The lower cavity was larger than the superior and its lower border approached the lower lobe. This cavity measured approximately 3 cm. in diameter and was separated from the smaller superior cavity by a septum. In the apex numerous bronchiectatic cavities

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of a few millimeters in diameter were found, all of which had thin walls lined with a glistening surface. In the apex, heavy anthracotic pigmentation and fibrosis were found. No distinct nodular lesions were palpated in the upper or lower lobe. In the lower lobe there were extensive bronchiectases and several calcific foci.

The right lung was greatly enlarged and had adhesions covering the major part of the upper lobe. In the upper third of this lobe a huge cavity was filled with a brownish mass, typical for aspergillus. This cavity communicated through a narrow tunnel, of about 2 mm. in length and diameter, with a second cavity of approximately 3 cm. in diameter. The latter also was filled with the brown crumbly material, typical of a "fungus ball." The lining in both cavities was smooth and shiny. The wall of the major cavity was only 1 to 2 mm. thick in some parts and could be ruptured easily. The main bronchus contained a mixture of mucus and brownish material (aspergillus). In the upper lobe, close to the lower border of the cavity, a focus 15 by 10 mm. was found which had a peculiar shiny appearance, and was suspected to be a chondroma.

Gross diagnosis: Bilateral cavitary histoplasmosis, with extensive pleural adhesions and thickening and fungus ball in the cavity in the upper lobe of the right lung.

The main feature of the microscopic examination was progressive, chronic fibrosis of the lungs as a result of scarring of inflammatory disease. Numerous bronchiectases and bronchiectatic cavities were found, some of which showed the presence of aspergillus; others demonstrated caseation of the wall. H. capsulatum was present in the wall in addition to the aspergillus found in the lumen. This was an extremely advanced pulmonary lesion, as evidenced by scarring and bronchiectases.

CASE 2. This forty-seven year old white man was admitted to the Dunham Hospital on August 9, 1959, with a history of cirrhosis, chronic cholecystitis and questionable duodenal ulcer in 1955. In addition, there was a history of unresolved pneumonia with pleural effusion in 1956. At that time both PPD and histoplasmin skin tests were positive. Four months prior to admission, symptoms of weight loss, productive cough and hemoptysis developed, and their progression prompted his admission. Physical findings of interest revealed dullness at the apices of the lungs with rales, and a palpable liver. Anemia was present as were signs of moderate hepatic damage. Searches for acid-fast organisms in the sputum were repeatedly negative. Chest roentgenograms revealed an infiltrate in the upper lobe of the right lung. Following admission the cough and fever continued. Serologic studies for histoplasmosis were positive in titers up to 1 to 512. All cultures of sputum for H. capsulatum were negative. Treatment with amphotericin B was begun on September 19, 1959, and discontinued on February



Fig. 2. Case 2, surgical specimen. Chronic cavitary histoplasmosis with marked scarring in surrounding tissue and massive thickening of pleura. Brownish masses adherent to wall of cavity are visible.

12, 1960. No change was noted in the size of the cavity but laminograms revealed an intracavitary inclusion. An upper lobectomy of the left lung was performed on April 29, 1960, which was followed by a tailoring thoracoplasty on May 17, 1960. The patient was discharged on August 5, 1960, in good condition, clinically and radiologically. (Fig. 2, 3, 4 and 5.)

The resected upper lobe of the left lung was markedly shrunken, with pronounced thickening of the pleura, which in many parts measured up to 5 mm. in thickness and was extraordinarily firm due to fibrosis and hyalinization. In the apex there was a cavity 3 by 3.5 cm., the walls of which were covered by brownish crumbly masses, typical of the presence of aspergillus. The major part of this material had been removed at operation for culture and photography. The pulmonary tissue adjacent to the cavity was fibrotic, grayish in color except for a few areas in which bronchi could be recognized. The bronchi were markedly distended and the wall of the bronchi was massively thickened by inflammation. In some of these bronchi, even far distal from the cavity, the brownish masses of aspergillus were found, proliferating in the lumen of the bronchi.

Gross diagnosis: Severe chronic scarring of upper lobe of the left lung with bronchitis, bronchiectases and cavity filled by aspergillus. Extensive pleural thickening with hyalinization.



Fig. 3. Partial content of histoplasmic cavity in Case 2. Several species of aspergillus were grown from this material.

On microscopic examination this lung showed a picture analogous to Case 1 in all respects, with chronic fibrosis and distortion of pulmonary architecture, bronchiectases, caseation of some of the bronchial lining and numerous aspergilli in the lumen of the enlarged cavity. The only difference was

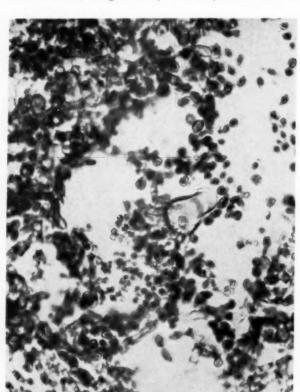


Fig. 5. Head of aspergillus in bronchial cast. Magnification X 800, hematoxylin and eosin stain.

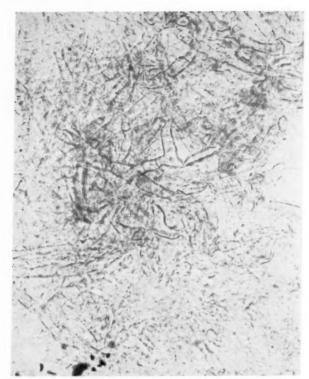


Fig. 4. Hyphae (of aspergillus) in sputum. Potassium hydroxide preparation, magnification X 600. Broad septate hyphae can be identified only by culture or demonstration of spores or other specific structures. See Figure 5.

that despite the examination of numerous specimens, histoplasma could not be demonstrated unequivocally in the tissue sections.

Case 3. This forty-nine year old white man was known to have had chronic obstructive pulmonary emphysema, chronic bronchitis and bronchiectases for many years. He had been hospitalized at the Veterans Administration Hospital, Cincinnati, three times prior to his final admission on September 14, 1959. All previous hospitalization had been for pulmonary insufficiency and occasional hemoptyses. Roentgenograms taken throughout his course revealed bilateral pulmonary emphysema with inflammatory disease of the upper lobes. Cavitation was suspected from the earliest film, dated 1956. Bronchograms revealed bronchiectases of the upper lobe of the right lung. (Fig. 6.) Sputum studies for acid-fast bacilli were negative on many occasions. During 1958 and 1959 the diagnosis of histoplasmosis was suspected because of serologic titers of complement fixing antibodies for histoplasmosis up to 1 to 512. Numerous sputum specimens were cultured for H. capsulatum but all were negative. His final admission was because of an increase in the symptoms of pulmonary insufficiency. His death occurred shortly after the injection of medication on September 15, 1959. At no time

during the patient's course was the presence of a fungus ball suspected.

At necropsy the lungs weighed 1,500 gm. and were covered by a greatly thickened pleura which adhered to the chest wall. In the right apex there was a fibrous area, with a cavity 2 cm. in diameter. Throughout both lungs there were numerous small nodules 2 to 3 mm. in diameter, some of which appeared to be calcified. Calcifications were found in the right hilar lymph nodes.

A large bronchus was traced in the upper lobe of the right lung. Brown, rather dry material, representing aspergillus, was present in the lumen of the cavity and bronchus.

Microscopic examination of the wall of the cavity showed extensive ulceration of the epithelium with H. capsulatum demonstrable in the necrotic area. In the lumen, aspergillus could be recognized. Adjacent to the wall of the cavity there were several caseated foci, each of which contained H. capsulatum. In other sections of the lung numerous caseous nodules were found, 3 to 6 mm. in diameter. The smaller ones frequently revealed a tendency to healing and were fibrocaseous. The larger ones showed mostly complete destruction of the elastic pattern and contained numerous organisms of H. capsulatum. In addition, a calcified primary focus was found with an osseous rim which contained numerous organisms of H. capsulatum. Several regional calcified lymph nodes showed the stippled calcification of histoplasmosis. Numerous organisms were found in the calcified regional lymph nodes. Examination of the fungus ball revealed several heads of aspergillus.

Case 3 is extremely interesting for several reasons. First, chronic cavitary histoplasmosis was present, complicated by the presence of a fungus ball in the cavity. Secondly, there was active disseminating histoplasmosis in the lungs, bronchogenic in origin in all likelihood, originating from aspiration of the cavitary contents. In the third place there was a completely healed and very old primary complex of histoplasmosis, implying that reinfection occurred sometime during the patient's course. Obviously, it is impossible with the available information to state whether this was endogenous or exogenous reinfection.

This man had lived on a farm all his life, and he must have had considerable exposure to spores of H. capsulatum. We assume that the primary complex was quite old since at least two morphologic facts point in this direction. One is the complete calcification and bone formation, the other is that the organisms in the primary focus and the regional lymph nodes stained with much less intensity than the organ-





Fig. 6. Case 3. A, chest roentgenogram showing bilateral nodular and linear densities in the upper lobes. B, bronchograms showing definite bronchiectases in upper lobe of right lung.

isms seen in active lesions. This we find to occur only when the organisms have been dead for many years.

Case 4. This seventy year old white man was admitted to the Veterans Administration Hospital, Cincinnati, in the summer of 1958 for a cataract extraction. At that time it was noted that he had bilateral cavitary disease of the upper lobes. (Fig. 7.) Studies for tuberculosis and all cultures were negative; the tuberculin skin test was negative up to 250 tuberculin units. Cataract extraction was accomplished and the patient was discharged, to return in the late fall of 1958 at which time the second cataract was removed. No change was seen in the pulmonary lesions. Following cataract extraction a histoplasmin skin test result was positive. Complement fixation studies for histoplasmosis revealed high titers. Several sputums were positive on culture for H. capsulatum. In early March 1959, treatment was begun with

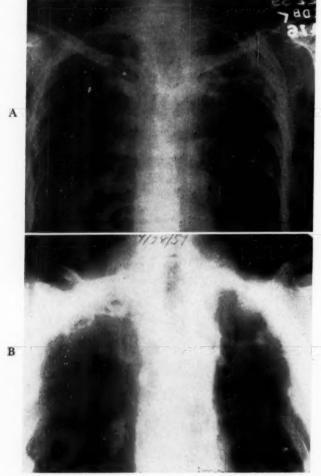


Fig. 7. Case 4. A, chest roentgenogram, showing bilateral disease in the upper lobes with cavity on the left. B, laminograph showing details of cavitary disease. These films were taken before fungus ball developed.

amphotericin B. This was continued until early June 1959, to a total dose of 870 mg. No change in the chest roentgenograms occurred. The patient was discharged and followed in the outpatient clinic. No change in the roentgenogram was noted from June to November 1959, at which time some filling of the cavity of the upper lobe of the left lung was seen. (Fig. 8.) Roentgenograms taken in February and May 1960 revealed further filling of the cavity. These spot films taken at fluoroscopy revealed the mass filling the cavity to be freely movable. (Fig. 9.) In May 1960, cultures of sputum were positive for H. capsulatum. These had been repeatedly negative for the preceding eleven months. The patient was therefore readmitted in early June and amphotericin B therapy was again begun. The patient was given 2,500 mg. In September 1960, he was discharged with little change evident on the chest roentgenogram, but with symptomatic improvement. Since discharge the patient has been well, with negative sputum cultures for H. capsulatum.

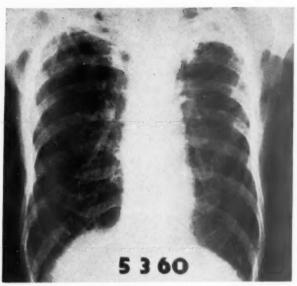


Fig. 8. Case 4. Chest roentgenogram after development of fungus ball in cavity of upper lobe of left lung.





B

Fig. 9. Case 4. A, spot film of upper lobe of left lung in left side down position. Note crescent air lying medially. B, patient in reverse position with left side elevated. Note the lateral location of the air crescent in this view.

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Comments: A few generalizations can be made concerning the four cases described. All were chronically ill white men. All were forty-five years of age or over. All had had chronic pulmonary inflammatory disease in the upper lobes for several years. All but one (Case 3) showed evidence of symptoms of progressive wasting. Hemoptysis was a prominent symptom in two of the four cases. It is of particular significance that there was nothing in the history, physical or laboratory data, except the cultures, to differentiate the chronic pulmonary inflammatory disease due to histoplasmosis from similar cases due to tuberculosis. It is of interest that the roentgenologic diagnosis of intracavitary fungus ball was made or suspected in three of the four

In three of the cases there was adequate anatomic evidence for the association of cavitary histoplasmosis and intracavitary fungus ball. In the fourth case, although the clinical and roent-genological impression could not be corroborated by the anatomic findings, there seems little doubt that the free-lying, movable, intracavitary inclusion was a fungus ball, most likely due to aspergillus infection. The histoplasmic nature of the cavity had been established by repeated positive cultures.

COMMENTS

The development of the fungus balls in the present cases was obviously secondary to severe underlying disease. All the patients had bronchiectases and bronchiectatic cavities, frequently with ulcerative endobronchitis and caseation necrosis of the bronchial wall. The aspergillus was always found merely lying upon the intact bronchial epithelium or upon the ulcerated wall without any penetration into the pulmonary tissue. One can come to the conclusion that the presence of the fungus ball prevents closure of the cavity and this may be a most undesirable side effect. It can be postulated then, in our Case 3, that bronchogenic dissemination almost certainly occurred from the cavity and it can be surmised that removal of the fungus ball by drainage or resection could have resulted in collapse of the cavity and potential healing. That this occurred in only one of the cases does not diminish the importance of this observation.

The role of aspergillus in the respiratory tract is not clear. This fungus is common but not to the exclusion of many other saprophytic

fungi. However, when the fungus producing the so-called fungus ball was at all identifiable, it almost always turned out to be a species of aspergillus, together with debris, bacteria, exudate and sometimes other fungi. Frequently the morphologic identification is dubious because the diameter of the hyphae found in the mycelial conglomerate within the pulmonary cavity is markedly greater than the width seen in culture mounts. The hyphal elements often look macerated, stain poorly, and the cytoplasm seems to have escaped. It is our impression that species of aspergillus enter cavities and proliferate very fast to a point where oxygen and nutritional requirements cannot be met, at least in the center of the proliferating fungal mass, where the fungus undergoes death and maceration.

Addition of gastric mucin to artificial media produced a marked increase of the hyphal diameter of several species of aspergilli. This may explain why aspergilli growing in bronchial mucus appear as noted.

The fungus ball, once formed, must largely depend in its development on the anatomic situation of the bronchus leading to the cavity. An open bronchus obviously will provide oxygen. Several of our patients expectorated large amounts of hyphae of aspergillus periodically, while at other times no fungus elements were present, which would indicate a valve mechanism or some other periodic bronchial occlusion.

It is unlikely that multiplication of the aspergillus organisms within the cavity would contribute to expansion of the cavity. It seems certain, however, that the fungus ball, once established within the cavity, prevents shrinkage and healing. The valve mechanism or bronchial stricture, which one has to postulate for the formation of bronchiectatic cavities in locations where postural drainage could be anticipated, very likely produces accumulation of mucus which over months or years results in formation of cavities.

The overwhelming majority of fungus balls (including those in our patients) complicating bronchiectatic and histoplasmic cavities are located in the apical regions of the upper lobes, where postural drainage should be at its best. This is in marked contrast to localization in the lower lobes of bronchiectases in general. When bronchiectases of the upper lobes do occur the underlying process (tuberculosis or histoplasmosis) results in narrowing constriction and distortion of the bronchi, with poor bronchial drainage

and perhaps poor aeration of the areas of lung involved, which may explain the apical location of the fungus balls.

SUMMARY

A review of recorded and our own experience with intracavitary fungus balls reveals aspergillus to be the most commonly identified fungus.

Such fungus balls are characterized roentgenologically by a crescent-like shadow above a movable ball-like structure. The cavities invaded by aspergillus most commonly are of bronchiectatic origin.

Four proved cases of cavitary histoplasmosis complicated by intracavitary development of aspergillus are presented herein.

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Pulmonary Hyaline Membrane Formation in the Adult*

A Clinicopathologic Study

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HYALINE membrane formation in the lungs of premature newborn infants is well recognized, and there are abundant excellent descriptions of this entity in the literature [1–6]. It is not so well recognized, however, that hyaline membrane formation occurs also in the lungs of adults, sometimes in a pure form, having been described in sporadic and widely isolated reports in association with a variety of conditions.

This article deals with a survey of lungs in adults over a period of three years, and includes selection of case reports from the autopsy files of the Dallas Veterans Administration Hospital. In addition, one case report submitted from the Kerrville, Texas, Veterans Administration Hospital is included. Early in 1960 lungs from all autopsy patients were studied by multiple section methods in order to determine the frequency, the clinical effects and the pathogenesis of hyaline membrane in adults. A total of thirty-seven cases, of which nineteen were focal and minimal and eighteen severe, form the basis for this study. The eighteen severe cases were subjected to more critical analysis.

MATERIALS AND METHODS

The autopsy files of the Dallas Veterans Administration Hospital for the years 1957, 1958 and 1959 were searched for the catalogued instances of hyaline membrane in the lung. Seven were located by this means and included in this study. In January 1960 a careful study of the lungs of all autopsy patients was commenced by taking sections from each lobe of both lungs. The tissues were fixed in neutral buffered formalin in separate containers for the right and left lungs. The tissues were dehydrated in slowly increasing ethyl alcohol and cleared in chloroform. Paraffin sections were cut at 4 to 8 μ and stained by the hematoxylin and eosin method. Lung sections in selected

cases were stained by the Mallory stain for fibrin to elucidate the nature of the membrane in the adult. In the severe cases, the sections were studied with special stains for fat by the Sudan Black and periodic acid-Schiff method. In addition, Perl's iron stain was used on lung sections from a single patient with aplastic anemia who had 192 sustaining blood transfusions.

Clinical data relating to the possible mechanisms of hyaline membrane formation were obtained and included the recording of blood urea nitrogen and serum protein values when available. Whether or not tracheostomy or some form of oxygen therapy was instituted was ascertained. The presence or absence of aspiration was recorded from a study of the lung sections for foreign material or foreign body granuloma formation [7]. The presence of associated pneumonitis was determined and a note of its type and severity was made when it was present. Anatomic data as to location of the hyaline membrane and the weights of the lungs were noted. The severity of involvement was graded microscopically according to membrane thickness, and the number of alveolar spaces involved per microscopic field.

FINDINGS

In the autopsy records for 1957 two cases of hyaline membrane formation in a total of 257 autopsies were found, a frequency of 0.73 per cent. In the 1958 autopsy series of 297, two cases again were found, a frequency of 0.68 per cent. In 1959, of 354 autopsies there were four instances of hyaline membrane, a frequency of 1.13 per cent. After more careful study by the multiple sections method in 1960 from a total of 352 autopsies, ten definite cases of hyaline membrane formation were discovered, a frequency of 2.76 per cent. In addition there were nineteen instances of minimal or borderline severity, recorded as 1 plus in degree of severity in the entire series of thirty-seven cases. In

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seventeen cases in all was marked hyaline mem-

brane deposition noted.

Location of Hyaline Membrane. The location of the hyaline membrane deposition could be determined in twenty-eight cases. The deposition occurred in the right lung only in six cases (15.7 per cent). The left lung only was involved in four (10.5 per cent) and both lungs were involved to some degree in the remainder of eighteen cases (73.8 per cent).

Relation to Tracheostomy. In seven of the thirty-seven patients with hyaline membrane formation a tracheostomy procedure had been performed, usually shortly before death. Four of these were associated with severe hyaline membrane formation and the remaining three occurred in patients with less severe involvement.

Aspiration in Relation to Hyaline Membrane. Histologic indications [7] of aspiration were seen in a total of six of the entire series. In one instance the aspirate material was hemorrhagic and presumably from bleeding about a tracheostomy wound. In all other instances the aspirated material was amorphous. Of the group with signs of aspiration, two occurred in patients with severe hyaline membrane formation, and the remaining four were found in patients with less severe involvement.

Relation of Hyaline Membrane to Serum Protein Levels. The serum protein levels were determined in eight patients of the entire series. The values ranged from 4.9 to 8.8 gm. per cent. The single patient with the elevated serum protein of 8.8 gm. per cent had a more severe type of hyaline membrane formation. All others had normal levels and the severity of the hyaline membrane was considerably variable and inconstant.

Relation of Blood Urea Nitrogen to Hyaline Membrane. The blood urea nitrogen concentrations were available in fourteen instances. The range was 6.8 to 200 mg. per cent. There were three patients with individual values of 94.2, 135 and 200 mg. per cent. The patient with the highest value (200 mg. per cent) had 2 plus involvement, and the patients with values of 94.2 and 135 mg. per cent had 4 plus and 1 plus involvement, respectively.

Relation of Hyaline Membrane and Oxygen or Oxygen Alevaire® Administration. Oxygen alone or in combination with Alevaire was administered at some time during the patient's final illness and hospital stay in thirteen instances. Five patients of the group had the more severe type of

hyaline membrane and one of this latter subgroup had associated intermittent positive pressure breathing. It would appear that this factor is of some significance for the development of the membrane.

Sex and Racial Factors in Hyaline Membrane. Occasionally a female patient is treated in the Dallas Veterans Administration Hospital, but in this survey covering the autopsy records for several years' duration, hyaline membrane was not found in the few female patients coming to autopsy. Of thirty-seven patients with hyaline membrane, four were Negroes and the remainder were Caucasians. None of the Negroes had the more severe type of hyaline membrane. The frequency of Negro subjects in the 1959 autopsy series was 15 per cent, so that of thirtyseven cases there would be a rough expectancy of perhaps five or six patients of the Negro race in this series if chance alone were operating as a factor. It is of greater significance perhaps that none of the patients with the severe or deathdealing type of hyaline membrane were Negroes.

Relation to Anesthesia. Two patients with severe hyaline membrane formation died suddenly under almost identical circumstances. These two patients were subjected to a thoracotomy procedure and lobectomy, one for pulmonary tuberculosis and the other for bronchogenic carcinoma. Each subject would be classed as young, and death occurred at approximately the same time interval after operation. Each of these patients had severe dyspnea and a feeling of apprehension immediately prior to death. A study of the anesthesia records in these cases reveals that cyclopropane anesthesia was used in both, along with some form of oxygen administration. Anesthesia was induced by pentothal in each, and Anectine® was used as an adjuvant.

Since these patients were anesthetized by different anesthetists, anesthetic technic would appear to have no relation to the membrane formation, but some anesthetic common to the two may have had some role in the development of the lesion.

Disease States Associated with Hyaline Membrane Formation. In the entire series of thirty-seven cases no particular or constantly recurring basic disease state was found as a common denominator leading to the development of hyaline membrane formation.

Some type of neoplastic process was present in thirteen patients (35.2 per cent). These were represented by six patients with bronchogenic

carcinoma, three of whom died of acute myocardial infarction. Other types of neoplasm were melanoma, squamous carcinoma of the larynx, primary carcinoma of the suprarenal gland, squamous carcinoma of the hypopharynx with a second primary carcinoma of the kidney. Hodgkin's disease was found in one case. One patient had a thymoma with myasthenia gravis. The hyaline membrane in this case was not severe.

A basic liver disease was noted in three patients. One of these had portal cirrhosis in association with mild hyaline membrane formation. In a second patient there was hepatic insufficiency; marked accumulations of fat were present in the liver, with moderate portal cirrhosis. The first and third of these patients had mild membrane formation, but the second had a fairly acute course clinically and marked deposition.

Cardiac disease occurred with fair frequency in patients of the series. Arteriosclerotic heart disease was noted in three; acute myocardial infarction or coronary thrombosis was noted in six, one occurring in a patient with bronchogenic carcinoma. Other basic diseases were rheumatoid arthritis and interstitial pneumonitis (one case), pulmonary tuberculosis treated by thoracotomy and segmental resection of lung (one case), accelerating nephrosclerosis (one case), chronic pyelonephritis with uremia (three cases), diabetes mellitus with peptic ulcer and acute pancreatitis (one case), and acute pancreatitis (one case).

When the patients with more severe deposition were isolated there was noted a strong association with neoplastic disease; eight patients had neoplastic disease of some type. The basic diseases are shown in Table 1.

Relation of Hyaline Membrane to Age. The age range for the patients in this series of thirty-seven cases was thirty-one to eighty years. In the group of eighteen patients with 3 to 4 plus hyaline membrane formation the age spread was thirty-one to seventy-four years. For the entire series the average age was 54.2 years. In the subgroup of severe cases the average age was forty-three years. This suggests the presence of an adaptive mechanism in the older subjects so that they are much better able to combat membrane production.

Relation of Antibiotic Administration to Hyaline Membrane. In eighteen cases it was noted that antibiotics were administered at some time,

Table 1
BASIC DISEASES IN HYALINE MEMBRANE FORMATION

Disease	No
Rheumatoid arthritis with interstitial pneumonia.	1
Carcinoma of bladder, radiation therapy	1
Arteriosclerotic heart disease with pulmonary	
tuberculosis	1
Accelerating nephrosclerosis	1
Myocardial infarction, cardiac massage	1
Bronchogenic carcinoma	2
Diabetes mellitus	1
Pulmonary tuberculosis with thoracotomy	1
Hepatic insufficiency	2
Squamous carcinoma of tongue, radical neck dis- section	1
Generalized malignant melanoma	1
Squamous carcinoma of left maxillary antrum	1
Bronchogenic carcinoma with myocardial infarc-	
tion	1
Hodgkin's disease	1
Carcinoma of hypopharynx with carcinoma of the	
kidney	1

usually in the final days of the patient's life. Two patients had the more severe type of formation. In some instances there was accompanying bronchopneumonia. Occasionally, membrane formation was seen in a field of bronchopneumonia, but this was a rare occurrence. It was much more usual to see the bronchopneumonia fields completely devoid of the membrane and the deposition outside of the pneumonia patches. This suggests (1) that the staphylococci or streptococci, common organisms in bronchopneumonia, have cleared the fields of membranes, and (2) that the material forming hyaline membrane is fibrin, since it is established that these organisms produce a profibrinolysin activator.

Pulmonary Edema in Relation to Hyaline Membrane. Edema fluid in alveolar spaces was occasionally encountered in the series. Usually, however, it was focal and not intimately associated with the membranes. More particularly, in the severe cases of hyaline membrane formation it was not encountered.

Relation of Blood Transfusion or Cardiac Overload to Hyaline Membrane Formation. In the subgroup of eighteen cases of severe or definite hyaline membrane the clinical records were reviewed to ascertain the possible relationship of blood transfusion to the membrane formation. Many of the patients in the series were cachectic, some from neoplastic disease, and presumably



Fig. 1. Case 32. Roentgenogram of patient after right thoracotomy and pneumonectomy for bronchogenic carcinoma. Pure hyaline membrane deposition was found at autopsy. Note left lung field, which has strong resemblance to that of pulmonary edema.

cardiac overload might develop when they were subjected to transfusions.

In the group of eighteen, there were eight subjects who had transfusions of whole blood. The number of transfusions of citrated whole blood ranged from 1 to 7 units in seven patients. One patient received 2 units of packed red cells on the same day. Thus 47 per cent (nearly half of the group) had transfusions at one time, usually shortly before death. In one case a patient had aplastic anemia and received 192 blood transfusions over a long period. The hyaline membranes in this patient were markedly positive for iron, showing that the material undoubtedly comes from the blood plasma. The amounts of transfusion and the severity of the membranes are noted in Table II. It would seem from these data that cardiac overload from transfusions may be a factor to be reckoned with in the development of hyaline membrane in adult lungs.

Radiation in Relation to Hyaline Membrane. The occurrence of hyaline membranes in human subjects treated with radiation has been described [8]. It has been suggested that oxygen poisoning and radiation have a common mechanism of releasing free radicals and decreasing SH

TABLE II
RELATION TO BLOOD TRANSFUSION

Case No.	Degree of Hyaline Membrane Formation	Amount (units)
1	++++	4
2	+++	5 (same day)
3	+	0
4	+	3 (same day)
2 3 4 5	++	0
6	+++	7*
7	2-3+	0
8	++	1
9	+++	0
10	+	0
11	3-4+	3
12	++++	2
13	++	0
14	++	0
15	++++	2 packed cells
16	3-4+	0
17	++	0
18	+++	192

^{* 5} on July 12, 1 on July 22 and 1 on August 15.

groups with consequent depolymerization of DNA as a possible mechanism in producing hyaline membrane [9,10].

This factor was evaluated in the critical series of hyaline membrane. In the group of eighteen cases, three patients had a history of radiation therapy. Two of these were to the chest or hilar region for treatment of inoperable bronchogenic carcinoma. A third patient had radiation to the maxilla for a squamous carcinoma of the antrum.

Relation of Cortisone and ACTH to Hyaline Membrane. There seems to be no relation between the clinical administration of ACTH, cortisone or cortisone-like compounds to patients with hyaline membranes. In the series of eighteen cases of the severe type, these compounds were given to only two patients. However, it is possible that all these patients were in the stress state and that ACTH and cortisone could have been mobilized from natural deposits, altering the fibrinolysin-antifibrinolysin complex in favor of antifibrinolysin, and contributing to hyaline membrane formation.

Roentgenologic Changes in Hyaline Membrane Formation. The roentgenogram film of the lungs of a patient dying of hyaline membrane deposition after thoracotomy for bronchogenic carcinoma is shown in Figure 1. The change demonstrated in this case closely approximates



Fig. 2. Case 32. Left lung. Pure hyaline membrane deposition produces a beefy red or purplish red surface and no pleural density.

that of pulmonary edema, and consists of a diffuse infiltrate which extends outward from the hilar region of the lung in a fan-shaped manner to the pleural cover.

Gross Features of Lungs with Hyaline Membrane Formation. The lungs involved with hyaline membranes are fairly firm, bright purplish red, with moderate to marked reduction in crepitance. The pleura overlying the involved parenchyma is not changed and is transparent, unless there is an associated pneumonitis, when there may be localized opacity from fibrinous or purulent exudate depending upon the type of underlying pneumonitis. (Fig. 2.)

The average weight of involved lungs was 830 gm. The range for this series was 400 to 1,200 gm., depending upon the severity of hyaline membrane deposition and other factors such as the presence of an associated tumor or pneumonitis. In the more severe cases the average weight was 1,000 gm.

The Microscopic Morphology of the Hyaline Membrane. In the severe cases the hyaline membranes were easily detected. The membranes were composed of brightly eosinophilic strands of a delicately laminated material which sometimes was closely applied to alveolar walls. At other times the material was at a slight distance away from the alveolar walls. At no time did it form balls of material or interlacing strands, respectively, of organizing pneumonia or of pure uremic pneumonitis.

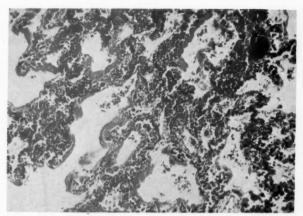


Fig. 3. Case 4. Low power magnification, hematoxylin and eosin stain. Note fairly thick hyaline membranes and no exudative reaction.

The strands of material tended to form a circular or half circular contour about the alveolar walls and frequently extended into the openings into the alveolar spaces. At times, long strands of the hyaline membrane were seen around the alveolar walls, projecting into alveolar stoma and adjacent alveolar spaces. (Fig. 3, 4 and 5.) The so-called septal cells were present beneath the membranes occasionally, but pools of protein of alveolar proteinosis [11] were not seen. Occasionally, epithelial cells were trapped in the membranes, but could not be identified with certainty as squamous in origin. The membranes were a delicate blue when stained by the Mallory PTAH method for demonstrating fibrin. In only one of the eighteen severe cases

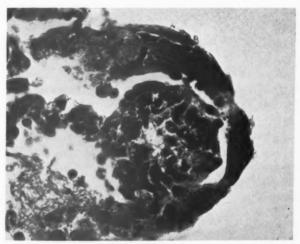


Fig. 4. Case 4. High power view, hematoxylin and eosin stain. Hyaline membrane is shown in more detail. It has trapped a few epithelial cells, some cellular debris and a few possible microorganisms. An alveolar spur is present in the center.

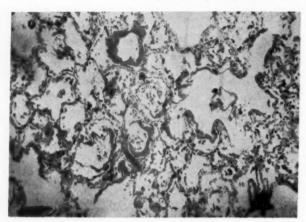
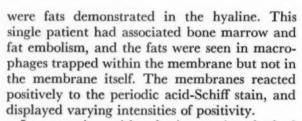


Fig. 5. Case 8. Low power magnification, lung section; hematoxylin and eosin stain. Hyaline membranes are densely formed, and tend to enclose attached epithelial cells.



In one patient with aplastic anemia, who had received 192 blood transfusions, there was moderate hyaline membrane, which contained many particles of fairly coarse iron throughout. (Fig. 6.) The membranes stained diffusely for iron as well.

The triad of hyaline membrane formation, vascular congestion and atelectasis occurring in newborn premature infants was not reproduced in the adult. Some degree of congestion was seen in a few sporadic cases, and congestion appeared inconstant in hyaline membrane in adults.

Atelectasis associated with a field of hyaline membrane deposition was present in only one patient in the subgroup of eighteen severe cases. Patchy atelectasis was seen in one other patient in the entire group of thirty-seven cases, and these areas of atelectasis were absent from the points of hyaline membrane deposition. Atelectasis, therefore, does not appear to be a general feature of hyaline membrane formation in the adult.

REPRESENTATIVE CASE REPORTS

CASE 4. Pulmonary tuberculosis with thoracotomy: A thirty-one year old white man (Dallas VAH, No. 71877) had a 40 pound weight loss, cough, night sweats and exertional dyspnea about five months before admission. Roentgenograms showed bilateral infiltration of both lung fields with cavitation in the

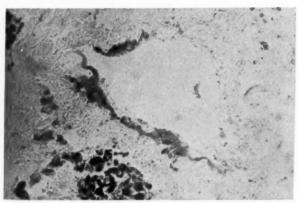


Fig. 6. Case 36. High power magnification, Perl's stain for iron. Hyaline membranes positive for iron are shown in greater detail, and contain scattered particles of iron, but also stain diffusely for iron.

right lung. He entered the McKinney, Texas, Veterans Hospital on April 11, 1958; a diagnosis of chronic pulmonary tuberculosis, far advanced, active, was made. He was scheduled for chest surgery on November 26, 1958; however, prior to surgery he went on pass from the hospital, was injured in an altercation, and was hospitalized in a private hospital. He returned to the Dallas Veterans Administration Hospital but was considered a poor candidate for major surgery, which was postponed. On physical examination he was a well developed, well nourished, white man, hostile and uncooperative, but mentally alert. Laboratory data were all within normal limits. Pulmonary function tests showed respiratory vital capacity 3.09 L., expiratory capacity 3.03 L., the one-second expiratory capacity was 2.55 L.

The patient was transferred to the Thoracic Surgery Service on December 10, 1958, was subjected to exploratory thoracotomy on the right, at which time an upper lobectomy and superior segmental resection of the right lung were performed, as well as a thoracoplasty resection of the second, third, fourth and fifth ribs on the right. In addition, a tip of the scapula was resected on the right. Postoperatively, the patient did well and gradually improved. On December 13, the third postoperative day, he began to complain of mild shortness of breath and had harsh rhonchi throughout the left side of his chest. Endotracheal suction was performed. The patient's abdomen became distended; gastric decompression was effected and small amounts of dark brown fluid were obtained. He was noted to have dyspnea and this became progressively worse. At 7:00 P.M. on the same day he began to have mottled cyanosis about the face and increase in respiratory excursions as well as rate. There was no chest pain and the respiratory rate was 50, blood pressure was 166/94 mm. Hg and pulse 140/minute. The dyspnea became worse when the patient reclined. A mild pitting edema of the ankles was noted. The heart rate was regular. At this time it was decided to give the patient digitalis,

but his deterioration progressed rapidly. A pleural rub was noted over the entire left anterolateral portion of the chest. Tracheostomy was performed, a tube was inserted, and the patient was given intermittent positive pressure breathing of oxygen, aerolone and alevaire mixture of 1:4. He improved somewhat but the tachypnea continued. He was then given 500 mg. of Terramycin® intravenously and 1 gm. of Chloromycetin® intramuscularly. His condition deteriorated considerably until 6:30 A.M. the next day. Roentgenograms showed diffuse haziness of the left lung at the junction of the middle and upper one-third. This haziness consumed about 50 per cent of the capacity of the left lung. The right lung appeared to be unchanged. The patient was started on heparin and an additional 0.4 mg. of Cedilanid® was given intravenously. At this time no serious venous distention was encountered. The patient was given massive doses of antibiotics. These measures did not help and he died on December 14, four days after thoracotomy.

At autopsy the right lung weighed 500 gm. and the left 900 gm. The left lung was purplish red and had a transparent pleura, except for some apical opacity. A few small foci of healing adult pulmonary tuberculous foci were present. The remainder of the entire lung displayed pure hyaline membrane deposition (Fig. 3 and 4), in contrast to the operative specimen of the lung which contained no hyaline membrane. There was a slight left pleural effusion. The heart appeared normal. The liver weighed 2,300 gm. and showed moderate fatty metamorphosis.

Case 8. Hepatic insufficiency: A thirty-one year old white man (Dallas VAH, No. A3135), a known chronic alcoholic, had an eight-month history of progressively decreasing appetite with weight loss and increased alcoholic intake. He became weak two months before admission, and was unable to stand. He had grand mal seizures unrelated to time of day, meals, drugs or other precipitating causes. A mild pitting edema of the ankles was present. Liver function tests disclosed 4-plus cephalin flocculation and 16 per cent bromsulfalein retention at forty-five minutes. The serum alkaline phosphatase was 5.2 Bodansky units, and the result of the spinal fluid examination was normal. After two to three weeks he began to go downhill (this had occurred on five previous hospital admissions) but this time he had shaking chills, dark urine and jaundice. He had intermittent watery, dark brown diarrhea. (His first episode of jaundice was in China in 1947; he began to drink heavily in 1951.)

On physical examination, the liver was enlarged. A grade 1 systolic murmur was present over the entire precordium but was loudest at the apex. The blood urea nitrogen was 16.7 mg. per cent, and the prothrombin time was 89 per cent of normal. The serum total protein was 5.1 gm./100 ml. The serum electrolytes were: sodium 130 mEq./L., potassium 2.2 mEq./L. and bicarbonate 26 mEq./L. A malaria smear of blood was negative. The white cell count

was 5,500/cu. mm., differential count: 8 bands, 58 neutrophils, 40 lymphocytes and 1 monocyte. The red cell count was 1.32 million/cu. mm., and the hemoglobin 5 gm./100 ml. A bleeding time was one and a half minutes, and the Lee-White clotting time was twenty minutes. The blood count was platelets 222,000/cu. mm. Hematocrit was 15.5 per cent, and the blood indices were mean corpuscular volume 117.4, mean corpuscular hemoglobin 37.7, mean corpuscular hematocrit 32.2. The reticulocyte count was 3.1 per cent. The patient was placed at bed rest on 70 gm. protein high caloric diet and with interval feedings. Hypokalemia was corrected with potassium added to an intravenous glucose solution. The patient had grand mal seizures twice during his hospital stay. The temperature rose to 102° to 104°F., but the chest remained clear of rales and dullness. The patient coughed but brought up no sputum, He was given penicillin, 600,000 units intramuscularly each eight hours. Roentgenograms of the chest disclosed bilateral pulmonary infiltrate in the upper lobes. The patient produced an icteric sputum at this time and antibiotic therapy was changed to streptomycin. The patient became more dyspneic and was continued on oxygen inhalations. He died on January 5, 1960; the admission date was December 28, 1959.

At autopsy each lung weighed 1,000 gm. and was beefy red in appearance. No fluid exuded when the lungs were palpated. Microscopically, the lungs had a severe hyaline membrane deposition, superimposed upon a mild chronic interstitial pneumonitis. (Fig. 5.) The liver showed marked fatty metamorphosis, some bile plugging of bile canaliculi and early portal cirrhosis.

CASE 5. Myocardial infarction: A sixty-one year old white man (Dallas VAH, No. A3136) saw an internist for a yearly check-up about six months before admission to this hospital; he was found to have an elevated blood pressure and was given Serpasil.® He did well following therapy and there was some lowering of blood pressure until two months before admission when he began to have anterior chest pain for the first time. This pain radiated over the left anterior portion of the chest and was associated with a constrictive feeling and fairly severe dyspnea. The patient entered an outside hospital where he was found to have myocardial infarction and mild congestive failure. He was given a low salt diet, Coumadin® and digitalis and responded well. He was discharged two and a half weeks later with subjective improvement. One week before admission to the Dallas Veterans Hospital he began to have some emotional stress and anterior chest pain developed again, although it was not as severe as before. He began to have nausea and became anoretic, and entered the Dallas Veterans Administration Hospital. The electrocardiogram showed numerous premature ventricular contractions and therapy with digitalis was discontinued. The patient denied having had polyuria, nocturia, dysuria,

frequency, urgency or back pain. There was no diarrhea, melena, hematemesis, cough or hemoptysis. The patient had smoked two to three packs of cigarettes daily for the past fifteen to twenty years. There was no habitual drug intake. He had consumed a half pint of whiskey every two or three days for the two months prior to admission. No allergies or drug sensitivities were present. The blood pressure was 110/70 mm. Hg; the pulse was 100/minute and regular. The throat had mild posterior pharyngeal injection. The lungs were normal except for a few moist rales bilaterally in the base of both lungs. The liver edge was found 4 fingerbreadths beneath the right costal margin. Pitting edema of the ankles was absent. The neurologic examination was within normal limits. The white blood count was 7,150/cu. mm., the differential count was 74 neutrophils, 4 bands, 22 lymphocytes; the red blood values were 11 gm. hemoglobin/100 ml., the corrected sedimentation rate 32 mm./hour and hematocrit 34 per cent. The urine had a trace of albumin and occasional granular casts, and many hyaline casts and a few leukocytes per high power field. The C-reactive protein was 4 plus; the result of the serologic test for syphilis was negative; the prothrombin time was 62 per cent of normal, and clotting time (Lee-White) was fifteen minutes; the serum transaminase was 470 units. The blood chemical values were: serum sodium 136 mEq./L., serum potassium 5.4 mg./100 ml., serum carbonate 36 mEq./L., serum chlorides 90 mEq./L., calcium 9.6 mg./100 ml. and phosphorus 5.6 mg. per cent. The serum total protein was 6.9 gm./ 100 ml. The electrocardiogram disclosed old anterolateral myocardial infarction with left axis deviation. One and a half hours after admission to the hospital the patient became cyanotic and had increased tachypnea with a subjective feeling of discomfort on breathing; the venous pressure was 21 mm. H₂O and the circulation time, arm to tongue, was forty seconds. The patient was given potassium chloride, 1 gm. three times daily and oxygen inhalation. The cyanosis cleared somewhat but on July 27, 1959, tachypnea increased again and the patient again became cyanotic and was unresponsive. The blood pressure was unobtainable and the pulse was 150/minute. Five per cent dextrose in water solution with 1 ampul of adrenalin added was given. Two hours later the blood pressure was 120/74 mm. Hg, and the pulse 120/minute and stronger. The patient became more alert, felt better but was thought to have beginning pulmonary embolization. He continued downhill, became irrational and confused. The blood pressure again dropped and urinary output was less than 500 cc. for the next twelve to fifteen hours. Intermittent positive pressure breathing with alevaire and nebulization was commenced. The patient later became unresponsive and markedly cyanotic. The respirations appeared agonal, and the patient died on July 27, 1959; the admission date was July 26, 1959.

At autopsy the right lung weighed 650 gm. and the

left 800 gm. Each was brownish red and microscopically had moderate hyaline membrane deposition, similar to that in Case 8. (Fig. 5.) The heart showed left ventricular hypertrophy, an area of recent myocardial infarction and a mural thrombus of the left ventricle. All other viscera exhibited changes of acute and chronic passive hyperemia. There was arteriolar nephrosclerosis.

COMMENTS

Descriptions of hyaline membrane as it exists classically in newborn infants are numerous [1–6]. In infants, hyaline membrane formation is considered an entity occurring in premature newborn infants, and morphologically shows in addition to hyaline membrane deposition in the lungs, two other portions of a triad—marked atelectasis and severe vascular congestion. Usually these alterations have been described as widespread throughout the lungs.

The various theories that have been advanced to explain the occurrence of hyaline membrane in the lungs of newborns fall into two common groups: (1) the hyaline membrane is deposited from aspirated amniotic fluid, or (2) the material is protein that passes from alveolar wall capillaries across both capillary and alveolar lining basement membranes, where it is deposited as a band or layer around the alveolar walls. Others have suggested that the material in part is secreted by alveolar lining or terminal bronchiolar epithelium [10,12].

Recently, by two new approaches the hyaline membrane has been demonstrated to be, without doubt, composed of a meshwork of closely placed fibrin strands. In electron microscopic studies of the membrane in the lungs of infants, Van Breemen, Neustein and Bruns [13] have shown that the pattern is identical with that of fibrin clots subjected to the same means of study. Gitlin and Craig [2] have reached similar conclusions by utilizing the fluorescent antibody technic in which the membrane reacts positively for fibrin. The present study indicates that the material as it occurs in the lungs in adults also is fibrin.

From this study it would seem best at present to consider hyaline membrane formation in adults a transudative phenomenon rather than the result of inhalation of aspirated material or secretion of alveolar lining cells. This would seem to be supported by findings of evidence of aspirated material in but a few instances of hyaline membrane in the total series of thirty-eight cases (six of thirty-six cases) and two of

eighteen patients with severe membrane formation. The finding of iron in hyaline membranes of a patient with aplastic anemia receiving 192 blood transfusions indicates that the material comes from plasma.

Various mechanisms and etiologies have been proposed and considered in connection with hyaline membrane in infants. These include oxygen poisoning [10], anoxia of some form [14], pulmonary edema, aspiration of amniotic fluid and vernix caseosa [15] and disturbance in pulmonary vasomotor function [10,16,17] among others. Some have suggested a virus infection [3]. Lendrum [18] views hyaline membrane formation in infants as a manifestation of left-sided heart failure and that this failure imposes an extra load on a marginal pulmonary vascular bed.

Experimentally, vagotomy in rabbits [16,17], oxygen poisoning [10], carbon dioxide poisoning [10], and intratracheal injections of foreign material including India ink, amniotic fluid and plasma or amniotic fluid with calcium chloride have been used to produce hyaline membrane formation in rabbits [1,2,15,19]. None has been a completely successful means of producing hyaline membrane, although Alvizouri [20] claimed a 100 per cent measure of success by intratracheal injection of plasma plus calcium chloride. More recently Lieberman and Kellogg [21] have demonstrated a complete lack of naturally occurring fibrinolysin in the lungs of a series of infants with hyaline membrane. Infants dying of other causes, but not having hyaline membrane, were shown to have normal amounts of pulmonary fibrinolysin. This work seems to provide a promising clue in clearing the mystery of hyaline membrane formation both in infants and in adults. It follows from this demonstration that hyaline membrane may occur in infants with normal amounts of fibrinolysin but is likely to be cleared immediately. In infants with absence of pulmonary fibrinolysin a mechanism is not available for resolution of the membranes. It is possible that all premature infants may have some degree of hyaline membrane at birth. There is also the intriguing possibility that a similar lack of fibrinolysin may occur in the lungs of adults to explain the occurrence of hyaline membrane. On this assumption, the fibrin deposition in hyaline membrane of the lungs of adults could be the result of transudation of protein-bearing fluids from alveolar wall capillaries into alveolar spaces. Adults with normal fibrinolysin could conceivably clear the

fibrin as it occurs before serious consequences arose. Those adults with the membrane might lack the clearing fibrinolysin.

The initial capillary-damaging stimulus might occur in a variety of basic disease processes, but might fundamentally be anoxia of any source [14]. Mechnical factors may also be implicated in the pathogenesis of hyaline membrane. Overoxygenation or oxygen poisoning cannot be entirely discounted as a cause for hyaline membrane formation. In this series fourteen of eighteen patients with severe hyaline membrane formation had some form of oxygen inhalation, either alone or with alevaire or intermittent positive pressure breathing.

One other point deserves consideration. In the severe cases of hyaline membrane deposition nine, or half of the subgroup, had some type of associated pneumonitis. Usually this was a suppurative pneumonitis or bronchopneumonia. Except for one instance the hyaline membranes were never seen directly in the areas of exudate formation, presumably because many of these bronchopneumonias are of staphylococcal or streptococcal etiology. It is known that these organisms may produce a profibringlysin activa-

streptococcal etiology. It is known that these organisms may produce a profibrinolysin activator, designated staphylokinase or streptokinase [22] and therefore may have cleared the exudative areas of hyaline membrane deposits.

Radiation has also been cited as one of the factors in the production [8]. Hyaline membranes have been found in the lungs of human subjects treated with radiation in whom radia-

branes have been found in the lungs of human subjects treated with radiation in whom radiation damage may affect the respiratory cells rather than the capillaries. Oxygen poisoning and radiation may act through a common mechanism of causing free radical formation with consequent inactivation of SH groups, denaturation of free enzymes and depolymerization of nucleic acids [9,23]. In the analysis of this series of patients with hyaline membrane three of the eighteen patients had some form of radiation therapy; two of these were directly to the lung field. It would thus appear that radiation is of no great significance in the production of hyaline membrane.

Hyaline membrane is said to be deposited occasionally in so-called uremic pneumonitis [24]. In this series hyaline membrane deposition rarely occurred in patients with uremia.

Clinically, the patients with hyaline membrane exhibit marked dyspnea with cyanosis, and are extremely apprehensive when conscious. Respiratory rates are elevated and respiratory movements are violent in order to overcome the defect. Roentgenograms of patients with pure hyaline membrane have been interpreted as

showing acute pulmonary edema.

Since atelectasis is not a feature of hyaline membrane in adults it would seem that the major clinical effects are due to the hyaline membrane barrier preventing exchange of respiratory gases across the alveolar epithelium and basement membranes into the pulmonary circulation. Possibly the addition of fibrinolysin to aerosol inhalant in conjunction with cardiac drugs may benefit these patients.

SUMMARY

The formation of hyaline membrane in the lungs of adults is demonstrated in a series of thirty-seven cases occurring at the Dallas Veterans Administration Hospital over a period of three years. Eighteen of these were severe and death was due chiefly to respiratory failure.

It is suspected that hyaline membrane formation in adults is basically similar to that occurring in infants, and that there is a lack of fibrinolysin in the lungs of adults to clear hyaline membrane as it may develop in a variety of clinical disease states. This, however, remains to be demonstrated.

Pulmonary hyaline membrane deposition in adults differs in major respects morphologically from that seen in infants, since it is not constantly accompanied by atelectasis. It is considered to be a transudative phenomenon. The qualitative difference between pulmonary edema and hyaline membrane in adults, however, could be explained by differences in the fibrinolysin content of the lungs.

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Left Superior Vena Cava*

A Review of Associated Congenital Heart Lesions, Catheterization Data and Roentgenologic Findings

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A LEFT superior vena cava is not often discovered during cardiac catheterization, but its presence may complicate cardiac catheterization when undertaken from the arm. We have encountered this anomaly in thirty of 786 patients referred for investigation of heart lesions. In this report we wish to draw attention to the way in which the left superior vena cava was recognized, the anatomic connections of the vessel, complications associated with cardiac catheterization, and surgical considerations.

EMBRYOLOGIC CONSIDERATIONS

The relevant embryology has been reviewed by a number of authors [1-5]. The origin of the left superior vena cava may be attributed to the persistence of the left anterior cardinal vein together with its caudal junction with the left duct of Cuvier. Blood from the left vena cava in such instances returns to the right atrium by way of the coronary sinus. Less frequently the ostium of the coronary sinus may fail to develop, resulting in blood from both coronary sinus and left superior vena cava entering the left atrium and thus giving rise to central cyanosis. Finally, a persistent anterior cardinal vein may empty directly into the left atrium, again causing central cyanosis. In this instance, the coronary sinus is usually normal in origin and termination.

Although a left superior vena cava commonly drains only the left side of the head and neck and the left arm, blood from the lower part of the body may also enter this vessel. Abnormal persistence of parts of the subcardinal system of veins on the left may result in the formation of a large venous channel lying parallel to and to the left of the spine. This continues above the dia-

phragm as a large accessory hemiazygos vein, which empties into the left superior vena cava between the termination of the left subclavian vein and the origin of the coronary sinus. The added volume of blood in such a left superior vena cava may present special problems when venous cannulation is attempted in preparation for extracorporeal circulation in the course of cardiac surgery.

A further relevant consideration is the development of the left innominate vein which first appears as a venous channel joining the two anterior cardinal veins. The absence of such a communication leads to difficulties in catheterization from the left arm as the catheter enters the right atrium in an unusual way.

INCIDENCE AND ASSOCIATED ANOMALIES

These 786 patients included eighty-three patients with rheumatic heart disease. These eighty-three patients were catheterized, but no instance of left superior vena cava was found. The presence of other congenital anomalies was established in twenty-nine of the thirty patients with left superior vena cava; no associated lesion was discovered in one.

In twenty-seven of our thirty patients the left superior vena cava was discovered during cardiac catheterization or angiocardiography. In two, it was not found until necropsy, and in the remaining patient its presence was demonstrated at operation.

The nature of associated congenital heart lesions was proved in twenty-seven patients. Convincing clinical evidence justified a diagnosis of congenital aortic stenosis in one of the remaining three (patient 141), and idiopathic dilatation

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TABLE I

Case No.	Sex and Age Associated Congenital Anomalies (yr.)		Course of Left Superior Vena Cava	Diagnostic Confirmation		
952	F,11	Normal heart	Coronary sinus	Catheterization		
791	F,10	Idiopathic dilatation pulmonary artery	Coronary sinus	Catheterization		
969	F,16	Atrial septal defect	Coronary sinus	Catheterization		
350	F,4	Atrial septal defect	Coronary sinus	Catheterization, op		
61	F,5	Atrial septal defect	Coronary sinus	Catheterization, an giocardiogram		
181	F,22	Atrial septal defect	Coronary sinus	Catheterization		
315	F,42	Atrial septal defect	Left atrium	Catheterization, autopsy		
289	F,42	Atrial septal defect	Coronary sinus	Catheterization, op		
131	M,2	Ostium primum	Coronary sinus	Catheterization, op- eration, autopsy Catheterization		
774	F,10	Ostium primum	Coronary sinus			
199	M,3	Atrial septal defect; left hemiazygos to left superior vena	Left atrium	Catheterization, operation Angiocardiogram,		
276	M,9/12	Atrial septal defect; anomalous pulmonary veins to left	Innominate, right superior vena cava	operation, autopsy		
255	F,13	superior vena cava Atrioventricular canal (complete form); accessory hemi-	Coronary sinus, left	Catheterization, and		
233	F,13	azygos to left superior vena cava	atrium	giocardiogram, op- peration, autopsy		
291	F,15/12	Atrioventricular canal; left superior pulmonary veins to left superior vena cava	Coronary sinus	Autopsy		
158	M,2	Ventricular septal defect	Coronary sinus	Catheterization		
303	F,9	Ventricular septal defect	Coronary sinus	Catheterization, op- eration		
141	M,5	Suspected congenital aortic stenosis	Coronary sinus	Catheterization		
180	M,6	Atrial septal defect; ventricular septal defect; anomalous pulmonary vein to right superior vena cava	Coronary sinus	Catheterization, op- eration		
258	F,6	Ductus arteriosus; single coronary artery	Coronary sinus	Catheterization, op- eration, autopsy		
290	M,2	Trilogy of Fallot	Coronary sinus	Catheterization, op- eration Catheterization		
685	M,9	Pulmonary stenosis	Coronary sinus	Catheterization		
351 88	M,36 M,41	Pulmonary stenosis; atrial septal defect	Left atrium Coronary sinus	Catheterization		
187	M,41 M,4	Tetralogy of Fallot Tetralogy of Fallot; anomalous pulmonary veins to right atrium	Coronary sinus	Catheterization, op- peration, autopsy		
243	F,5	Tetralogy of Fallot; foramen ovale	Coronary sinus	Catheterization		
341	F,5	Tetralogy of Fallot; accessory hemiazygos to left superior vena cava; anomalous pulmonary veins to right atrium	Coronary sinus	Catheterization, op- eration, autopsy		
459	M,6/12	Tetralogy of Fallot; patent foramen ovale	Coronary sinus	Catheterization		
563	M,5/12	Tetralogy of Fallot; suspected ductus arteriosus	Coronary sinus	Angiocardiogram (left arm)		
322	F,16/12	Tetralogy of Fallot		Operation		
540	M,2/12	Single ventricle; atrial septal defect; truncus arteriosus; two pulmonary arteries from ductus; inferior vena cava to left of abdominal aorta; left pulmonary vein to hepatic vein; right pulmonary vein to inferior vena cava; situs inversus of liver, spleen, stomach		Autopsy		

of the pulmonary artery was the sole abnormality in another (patient 791). The third patient (952) appeared to have no associated abnormality. The various associated lesions are listed in Table 1.

Thirteen patients were cyanotic and of these, cyanosis was attributable to intracardiac shunts in eight. In the remaining five, cyanosis resulted from drainage of venous blood into the left atrium. The left superior vena cava entered the left atrium directly in four of these five patients, and in the remaining patient (255) a persistent common cardinal vein entered the coronary sinus, which in turn communicated with both left and right atria.

Steinberg [6] estimated that a left superior vena cava was present in 0.5 per cent of the population. From a review of reports on the subject, Sipila [4] suggested that about 10 per cent of all patients with congenital heart disease have a left superior vena cava. Campbell and Deuchar [5] found this vein in only 3 per cent of 1,500 patients with congenital heart disease when those with transposition of the great vessels were excluded. The incidence of left superior vena cava in our patients with congenital heart disease was 4.3 per cent, a finding which agrees closely with that of Campbell.

ROENTGENOGRAMS

Gensini et al. [3] have reviewed the roent-genographic findings in patients with left superior vena cava: they measured the width of the vascular pedicle and related this to thoracic diameter in order to obtain a ratio. A comparison was then made between the ratios found in patients with left superior vena cava and normal control subjects. A statistically significant difference was found between the ratios measured in these two groups. While the statistical validity of this observation is not questioned, we did not find measurement of this ratio consistently helpful in individual patients in our series.

While reviewing the posteroanterior chest roentgenograms of patients known to have left superior vena cava, we observed a crescentic vascular shadow passing from the upper left border of the aortic arch toward the middle third of the left clavicle. Roentgenograms taken with the cardiac catheter in the left superior vena cava demonstrated that this crescentic shadow was formed by the lateral border of this vessel. In



Fig. 1. A cardiac catheter is shown passing down a left superior vena cava to the left atrium and thence to the right inferior pulmonary vein.

Figure 1, a catheter is shown passing through a left superior vena cava to enter the left atrium (patient 199). The border of the vein can be seen lateral to the catheter at the level of the aortic arch. Figure 2 is taken from patient 351 following a transthoracic left ventricular puncture. A small apical pneumothorax resulted and the crescentic border of the left superior vena cava can be seen against the background of air. A further demonstration of the vein is illustrated in Figure 3.

When posteroanterior chest roentgenograms of the thirty patients in our series were examined, we concluded that the sign described was definitely present in fifteen, questionable in four and absent in the remaining eleven. This suggests that in the majority of patients with left superior vena cava, evidence for the presence of this vessel will be found on the chest roentgenogram.

CARDIAC CATHETERIZATION

Catheterization from the left arm is more likely to lead to recognition of a left superior vena cava than catheterization by other routes. An advantage of entering this vessel has been the demonstration of anomalous pulmonary veins draining into it. A disadvantage has been the problem of completing cardiac catheteriza-

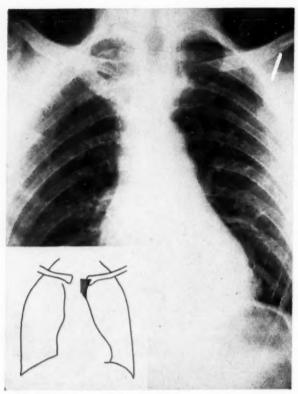
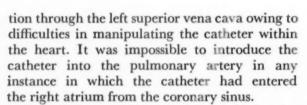


Fig. 2. Note the crescentic border of the left superior vena cava, accentuated by a left apical pneumothorax (patient 351).



Complications arising in patients during the course of cardiac catheterization through a left superior vena cava appear to be more common than in patients catheterized through a right superior vena cava. Catheterization of the coronary sinus is necessary in order to reach the right atrium and has, on occasion, been thought to result in shock [7]. Heager [8] reported cardiac arrest during cardiac catheterization of a patient through a left superior vena cava. However, he attributed this to irritation of the vagus nerve during manipulation of the catheter at the junction of the subclavian vein and the left superior vena cava. Neither of these complications was encountered in our series, but one patient (315) complained of anginal pain similar to that described by McMichael and Mounsey [7]. The pain began when the catheter was introduced into the coronary sinus and

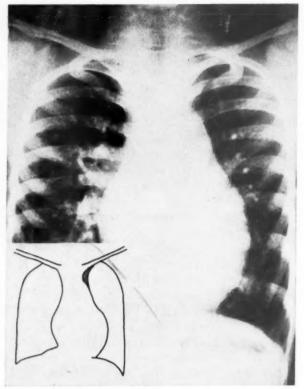


Fig. 3. Left superior vena cava demonstrated in patient 303.

lasted for thirty minutes. The subsequent course was uneventful.

The production of supraventricular tachycardia is not uncommon in any large series of cardiac catheterizations. Of our patients submitted to catheterization, in whom the catheter was passed down a right superior vena cava, supraventricular tachycardia occurred in 7.9 per cent. In contrast, supraventricular tachycardia was induced in 38 per cent of our patients with a left superior vena cava. In no instance did tachycardia have serious results, although some attacks persisted for several hours.

Difficulty in passing the catheter from the left subclavian vein to the midline was often experienced and we have come to regard this as suggestive evidence for the presence of a left superior vena cava. In six patients the catheter was first passed from the left arm only to enter a left superior vena cava. It could not be manipulated across the midline (through a communicating vein) to a right superior cava. Subsequently, however, the catheter was passed from the right arm and, in each instance, it crossed the midline through a venous communication and entered the left subclavian vein. The presence of a right

superior vena cava joining the right atrium in a normal manner was proved in each of these patients. Hence, failure to pass the catheter across the midline from the left side did not exclude the presence of a communication between the two venae cavae.

ANGIOCARDIOGRAPHY

This procedure has been particularly useful in outlining venous return from both superior and inferior vena caval systems in several of our cyanotic patients with left superior vena cava (patients 199, 255 and 341). Kjellberg [1] and Anderson [9] have each described patients with a left accessory hemiazygos vein emptying into a persistent common cardinal vein, which in turn drained into the left atrium. Similar abnormalities were demonstrated in patients 199 and 255. In patient 341 an accessory hemiazygos vein and a left superior vena cava joined to enter a normal coronary sinus, simulating the early embryologic pattern of these veins.

SURGICAL CONSIDERATIONS

Attention has been drawn to problems encountered during cardiac surgery resulting from the presence of a left superior vena cava [10]. Operations were performed on thirteen of our patients, cardiopulmonary bypass being used in twelve. When right and left superior venae cavae were present, the left was ligated only when an adequate communication had been proved to exist between the two vessels. As examples, in patient 255 the venous pressure in the left arm did not rise after ligation of the left superior vena cava; this was accepted as evidence for a communication with the right superior vena cava. In contrast, patient 303 had a very small right superior vena cava and the left superior vena cava, a much larger vessel, had to be used for cannulation. In all other instances in which the left superior vena cava emptied into the coronary sinus, the venous return was controlled by intracardiac suction or the left superior vena cava was temporarily occluded without ill effect.

The surgical problems arising in patients in whom a left superior vena cava enters the left atrium may be more complicated. If all the abnormalities can be accurately detailed before operation, it should be possible to decide whether to ligate the left vena cava or whether to transfer the point of entry of the vessel to the right side of

the circulation. In the case of a cyanotic three year old boy (patient 199), arterial oxygen saturation increased from 78 to 89 per cent after closure of an atrial septal defect, and ligation of both a left superior vena cava and an accessory hemiazygos vein at the point of entry into the left atrium. Despite a careful search for another systemic vein leading to the left, none was found. Postoperative cardioangiograms have not been obtained, but the patient now has no disability and only minimal cyanosis. All abnormalities of venous return in patient 255 were detected preoperatively through information obtained from catheterization and angicardiograms (contrast medium was injected into the left brachial and left saphenous veins).

In summary, our experience with the group of patients presented herein has led us to believe that a left superior vena cava can often be suspected on ordinary roentgenographic investigation. If other heart lesions coexist, complete delineation of the area drained by this vessel should be attempted as this information may be germane to the proper planning of appropriate cardiac surgery.

SUMMARY

Data from clinical, roentgenologic and catheterization studies on thirty patients with a left superior vena cava are presented. The incidence of this anomaly in a series of patients investigated for suspected congenital heart disease, from which these examples were obtained, was 4.3 per cent. In five patients a systemic vein drained directly into the left atrium. The difficulties encountered during catheterization through the left arm in such patients included a higher incidence of arrhythmias during the procedure and difficulty in introducing the catheter past the right atrium.

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Supravalvular Aortic Stenosis*

Clinical Experiences with Four Patients Including Familial Occurrence

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Supravalvular aortic stenosis represents a heterogeneous grouping of several morphologic entities, presumably congenital in origin. The most frequent lesion is a shelf-like thickening or ridge at the upper border of the sinuses of Valsalva, producing a circular narrowing of the aorta at this level. One or more aortic cusps may be involved with fibrous bands extending from the aortic leaflets to the obstructing ridge. This may result in aortic regurgitation or a restriction in the access to the respective coronary artery ostium, or both. In addition, a long narrowed segment of the ascending aorta may produce obstruction to the left ventricular outflow.

The clinical experiences with three young males and the female sibling of one of these patients constitute the basis for this report. All four patients manifested clinical evidence of aortic stenosis, significant systolic pressure differences in the arms and fluoroscopic evidence of left ventricular enlargement in the absence of poststenotic dilatation of the aorta. In addition to the supravalvular stenotic segment, pathologic or roentgenologic evidence of deformed aortic cusps or abnormalities of coronary filling, or both, were present in all four cases.

CASE REPORTS

CASE I. A thirteen year old white boy was admitted to the Children's Hospital, Columbus, Ohio, in October 1959 for surgical correction of aortic stenosis. A heart murmur had been first noticed at age five; symptomatology included moderate retardation of growth, progressive fatigability and exercise intolerance, with the recent onset of chest pain following exercise. There had been progressive left ventricular hypertrophy as shown by both roentgenogram and

electrocardiogram. No familial history of cardiac disease was elicited.

Physical examination revealed a slender, underdeveloped white boy in no distress. The blood pressure in the right arm was 80/60 mm. Hg; left arm 98/70 mm. Hg, right leg 100/64 mm. Hg and left leg 90/58 mm. Hg. There was a systolic thrill in the suprasternal notch and over both carotid arteries, and evidence of cardiomegaly. The aortic second sound was present and of decreased intensity. A grade 4 harsh, systolic ejection type murmur was heard over the entire precordium with the maximal intensity in the second right intercostal space and suprasternal notch. There was a difference in the pulses of the upper extremities consistent with the recorded blood pressures. Results of routine laboratory studies were normal. The electrocardiogram showed the pattern of left ventricular hypertrophy and notched P waves. Roentgenologic studies (Fig. 1) revealed slight cardiomegaly. mainly involving the left ventricle and the left atrium. The aorta was small and a marked discrepancy between the size of the left ventricle and aorta was apparent. The pulmonary arteries were prominent.

The preoperative diagnosis was aortic stenosis, either valvular or subvalvular in type, and surgery was performed on October 7, 1959. The ascending aorta was noted to be moderately hypoplastic with a discrete area of narrowing, approximately 5 mm. in diameter, just above the aortic valves. Utilizing extracorporeal circulation, hypothermia and cardiac arrest a diamond-shaped teflon cloth patch was sewn into a longitudinal incision across the area of constriction in an effort to enlarge the circumference of the aorta at this level. Following the insertion of the patch, the heart action was restored, but the heart failed shortly after conclusion of the extracorporeal circulation and the child died.

At necropsy (Fig. 2) there was marked left ventricular hypertrophy (19 mm.); the outflow tract of the left ventricle was adequate, and the circumference at

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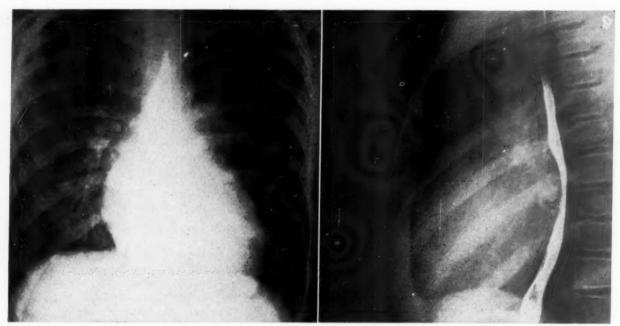


Fig. 1. Case i. Posteroanterior and lateral roentgenograms of the chest. The transverse diameter of the heart is slightly increased. The increased oblique diameter of the heart and the obliteration of the posterior inferior cardiac recess indicate left ventricular enlargement. The posterior displacement of the esophagus in the region of the enlarged left atrium is evident. The major branches of the pulmonary artery are prominent.

the level of the valves was 35 mm. Three aortic valves were present, however the margins of both coronary cusps were caught up into the ridge-like constriction at the upper margins of the sinuses of Valsalva. The width of constriction was approximately 3 mm., reducing the diameter of the aortic lumen at this level to 5 mm. The coronary arteries received blood through fenestrations 3 mm. in diameter, located in the upper central portion of the coronary cusps. The aorta beyond the constriction was hypoplastic, the circumference being 24 mm.

Comment: This case constituted our initial experience with this unusual entity and served to illustrate the pitfalls of assuming the diagnosis of congenital aortic valvular or subvalvular stenosis without benefit of angiography. It also served to suggest the diagnosis in the next case.

CASE II. A nineteen year old white male college student was referred to the University Hospital for evaluation of a heart murmur which had been present since childhood. His growth and development had been normal. There were no current symptoms; however, during adolescence the patient had experienced syncope and angina pectoris with marked exertion and had learned to avoid competitive athletics. Past history was otherwise non-contributory. Familial history indicated that the patient's mother had died of an undiagnosed cardiac disease at the age of thirty-seven. There were four healthy siblings.

Physical examination revealed a well developed,

muscular mesomorphic boy, 5 feet 7 inches in height and weighing 155 pounds. The blood pressure in the right arm was 100/70 mm. Hg, left arm 160/90 mm. Hg, both legs 200/110 mm. Hg. There was a marked discrepancy in the pulses of the upper extremities consistent with recorded blood pressures. There was a systolic thrill, maximal in intensity in the second right intercostal space, but also appreciated in the suprasternal notch and over both carotids. The second sound in the aortic area was diminished. A grade 4 harsh, low-pitched, ejection type systolic murmur was heard over the entire precordium, maximal in intensity in the second right intercostal space and suprasternal notch.

Results of routine laboratory studies were normal. The electrocardiogram showed the pattern of left ventricular hypertrophy. Fluoroscopy revealed moderate left ventricular hypertrophy and a small aorta. A left ventricular angiocardiogram was performed via the transfemoral approach (Fig. 3) which revealed thickening of the wall of the left ventricle and enlargement of this chamber. There was a narrowed segment of the ascending aorta above the aortic sinuses. The aortic valves showed increased thickness and impaired flexibility. The coronary arteries arose below the narrowed segment and filled simultaneously and equally. The remaining thoracic aorta was of smaller than normal caliber, however, the lumen was uniform. The left subclavian artery was 2 mm. larger in diameter than the right subclavian artery.

The direct pressure in the left ventricle was 278/0 mm. Hg; on catheter withdrawal there was an abrupt

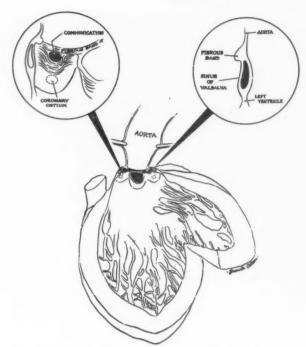


Fig. 2. Case I. Artist's sketch of the specimen at autopsy. The obstructing fibrous band was located at the upper margins of the sinuses of Valsalva and was 3 mm. wide. Three aortic cusps were present; however, the margins of both coronary cusps were caught up into the obstructing fibrous band (insert upper left). The coronary arteries received blood through communications, 3 mm. in diameter, in the upper central portion of the coronary cusps. The insert, upper right, illustrates the relation of the obstructing band to the sinus of Valsalva in a sagital view.

change to an aortic pulse contour with a pressure of 120/60 mm. Hg. The peak systolic gradient was 158 mm. Hg.

Comment: The clinical findings of aortic stenosis, the marked difference in the blood pressures and pulses of the upper extremities, and the absence of poststenotic dilatation of the aorta suggested the diagnosis. In this instance, and in the subsequent two cases, the radiologist was able to localize the difference in the pulses of the upper extremities from the aortogram without the clinical information. There was evidence of deformity of the aortic cusps without apparent interference with coronary filling. A supravalvular injection was not performed, hence, no comment regarding aortic regurgitation can be made.

CASE III. A sixteen year old asymptomatic white boy was admitted to the University Hospital for further evaluation of previously diagnosed congenital aortic stenosis. A heart murmur was first noted at six years of age. There was no history of rheumatic fever.



Fig. 3. Case II. Levocardiogram in lateral projection: the tip of the catheter is in the enlarged left ventricle which shows increased thickness of the papillary muscles. The marked narrowing between the aortic sinus and the ascending aorta above the level of the coronary orifice is well seen.

Of four siblings, one had aortic stenosis and is described (Case IV). The familial history is of interest in that the father was one of twelve children, six of whom died before three years of age. No postmortem examinations were performed, nor are any clinical diagnoses available.

On physical examination the patient appeared to be a well developed, muscular boy. The blood pressure was 140/70 mm. Hg in the right arm, 116/80 mm. Hg in the left arm and 140/70 mm. Hg in both legs. There was a systolic thrill in the second right intercostal space, in the suprasternal notch and over both carotid arteries. The apical impulse was mid-way between the left mid-clavicular line and the left anterior axillary line, in the sixth intercostal space. A grade 4 harsh, ejection type systolic murmur was heard over the entire precordium, neck and back, with maximal intensity in the third left intercostal space. The second sound in the aortic area was present and diminished. A grade 2 high-pitched, blowing, decrescendo diastolic murmur was heard along the left sternal border, best at the third left intercostal space. There was a gross difference in the pulses in the upper extremities consistent with the recorded blood

Routine laboratory studies were normal. The electrocardiogram showed the pattern of left ventricular hypertrophy. X-ray studies demonstrated left ventricular enlargement with a normal aorta. No evidence of



Fig. 4. Case III. Early anteroposterior levocardiogram. The short narrowed segment of the ascending aorta is partly obscured by the descending portion of this vessel. The left coronary artery fills by the injected contrast material before the visualization of the right coronary artery. The roentgenogram was taken in systole, the thickness of the wall of the left ventricle is impressive.

left atrial enlargement was noted. Utilizing the right femoral artery, a left ventricular angiocardiogram (Fig. 4 and 5) and a separate aortogram (Fig. 6) were performed. The injected contrast material outlined the enlarged left ventricle which demonstrated marked thickening of the wall. The outflow tract of the left ventricle showed no subvalvular narrowing. There was a consistent ring-like narrowing above both coronary arteries; the lumen of the aorta narrowed to less than 1 cm. at this level. The aortic cusps visualized well; the right aortic cusp was noted to be consistently deformed. There was normal filling of the dilated and tortuous left coronary artery; the right coronary artery showed a definite delay in filling. The ascending aorta measured 3.2 cm. in diameter, the innominate artery was also moderately dilated. The right subclavian artery measured 12 mm. in diameter as compared to the 6 mm. diameter of the left subclavian artery.

A second injection was made in the supravalvular region. (Fig. 6.) The injected contrast material showed mild regurgitation through the aortic valves into the left ventricle. There was prompt visualization of the left coronary artery but delayed and poor visualization of the right. The descending portion of the aorta was hypoplastic.

The direct left ventricular pressure was 300/0 mm. Hg while that in the proximal aorta was 170/90 mm. Hg, and that in the aortic arch 130/78 mm. Hg.

Comment: The clinical findings suggested the diagnosis. The severity of the obstruction was indicated by the excessive peak systolic gradient. The differential aortic pulse curve would seem to indicate that the catheter tip passed through the space between the cusps and site of the stenosis. The mild aortic regurgitation and delay in filling of the right coronary artery is presumed to be a manifestation of the consistent deformity of the right aortic cusp. The difference in blood pressures and the amplitude of the pulses in the upper extremities is again explained on an anatomic basis.

CASE IV. A nine year old white girl was admitted to the University Hospital for evaluation of known aortic stenosis. Her weight at birth was 8 pounds, following a full term pregnancy complicated by toxemia of pregnancy. The neonatal period was uneventful. A heart murmur had been known since infancy. Apparently she had been unable to keep up with other children. Her growth and development had been otherwise normal. Past history was significant in that the child had been treated for intermittent seizures related to exercise. She had an abnormal electroencephalogram. The patient is a sibling of the young boy referred to in Case III.

On physical examination the patient appeared to be a well developed, well nourished white girl. The blood pressure was 118/40 mm. Hg, in the right arm, 100/70 mm. Hg in the left arm, 128/76 mm. Hg in the right leg, and 130/80 mm. Hg in the left leg. She was 4 feet 4 inches tall and weighed 55 pounds. There was no evidence of cardiomegaly. A systolic thrill was palpable over the aortic area radiating to both carotid arteries. The aortic second sound was absent. A grade 4 harsh, low-pitched, ejection type systolic murmur was noted over the aortic area, with radiation into the neck vessels. A grade 2 high-pitched, soft blowing diastolic murmur was noted at the left third intercostal space, with radiation along the left sternal border. There was a gross difference in the pulses in the upper extremities consistent with the recorded blood pressures. No other physical abnormalities were noted.

Results of routine laboratory studies were normal. Cardiac fluoroscopy showed probable preponderance of the left ventricle. The aortic "knob" was noted to be small. The electrocardiogram was interpreted as showing probable left ventricular hypertrophy.

Utilizing the right femoral artery a left ventricular angiocardiogram and an aortogram (Fig. 7) were performed. The left ventricle was moderately enlarged. The outflow tract of the left ventricle showed no evidence of narrowing. There was a circular narrowing in the supravalvular area just above the level of the aortic cusps. Only two aortic cusps were seen on serial roentgenograms, which revealed normal filling

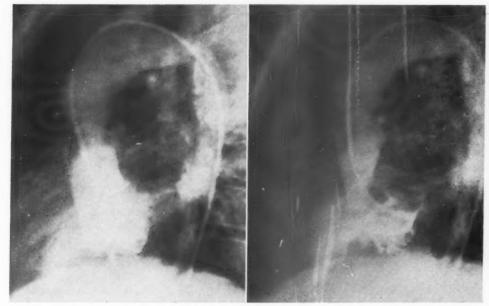


Fig. 5. Case III. Levocardiograms in lateral projection taken in diastole and systole. The narrowed supravalvular segment of the aorta is well demonstrated. The branches of the left coronary artery are filled, the right coronary vessel became opacified later on the follow-up roentgenograms. The ascending portion of the aorta measures 3.2 cm. in diameter against the 1.6 cm. wide caliber of the descending portion. The deformed right aortic cusp is demonstrated on this roentgenogram.

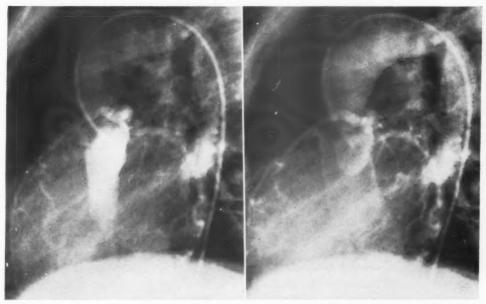


Fig. 6. Case III. Aortic valvulograms in lateral projection taken during diastole and systole: grade 1 regurgitation is demonstrated with almost complete disappearance of the contrast material from the left ventricle during systole (on the right). The dilated left coronary arterial branches and normal appearing right coronary artery are visualized.

of the dilated right coronary artery and slightly delayed filling of the smaller left coronary artery. Minimal aortic regurgitation was present. There was slight widening of the ascending aorta in comparison to the transverse diameter at the level of the aortic sinus. The right subclavian artery was wider in caliber than the left, with similar discrepancies in the lumens of the right and left axillary and brachial vessels.

The direct left ventricular pressure at the time of

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Fig. 7. Case IV. Lateral thoracic aortogram. The annular narrowing of the ascending aorta is well seen. The injected contrast material outlines only two valves, which have an anteroposterior relationship. The right coronary artery fills early. There was minimal regurgitation of the contrast material through the aortic valve.

this procedure was 150/0 mm. Hg, while that in the aorta was 98/48 mm. Hg. There was no area of transition on the pulse tracing comparable with Case III.

Comment: It is of interest that two siblings present with this unusual defect. Again the clinical findings suggested the diagnosis. Roentgenologic studies confirmed the defect; in addition a probable abnormality of the aortic cusps was demonstrated. Delayed filling of the coronary arteries was present and anatomic correlation of the inequality of upper extremity pulsations was obtained.

COMMENTS

Interpretation of this unusual clinical entity requires a review of the few previously documented cases. Discussions of this malformation usually include a number of cases of anomalous supravalvular aortic bands. Although these may be of interest from a morphologic or embryologic standpoint, associated clinical heart disease has been consistently absent. It is reasonable to assume that such abnormalities probably represent a developmental curiosity.

The nine cases reported by Mencarelli [1], Cheu et al. [2], Burry [3], Kreel and associates

[4], Denie and Verheught [5] and Morrow et al. [6] (three cases) constitute the existing clinical, pathologic, roentgenologic and surgical experiences with this malformation. Pertinent data from these reports are abstracted in Table 1. Mencarelli [1] was probably the first to describe this defect, gave it the current designation and considered the lesion congenital in origin. The case of Cheu et al. [2] is probably a related abnormality, but certain basic differences exist. Case 8 (Morrow et al. [6]) represents an example of a long stenotic segment of the aorta producing a similar result. Lev [7] mentioned the entity, included a photograph of a representative specimen, but did not amplify further.

The majority (six of nine) of these patients were males. The clinical findings were those of aortic stenosis, with the murmur of aortic insufficiency recorded on three occasions. In only two cases were the blood pressures recorded in both upper extremities, and in one of these (Case 8) a significant systolic pressure difference was noted. In only one case was poststenotic dilatation of the ascending aorta noted.

In our series three of four patients were males, all had findings of aortic stenosis and in two the murmur of aortic insufficiency was present. All patients had significant differences in blood pressures and pulses in the upper extremities. In only one patient (Case 3) was there equivocal evidence of poststenotic dilatation of the aorta.

Pulse tracings or pressures (or both) were recorded in four of the previously reported cases, significant peak systolic pressure gradients were noted four times. A characteristic track back tracing from left ventricle to aorta, revealing an intra-aortic pressure gradient, was obtained three times. Three of four patients in our series had excessive peak systolic ventricular aortic gradients and one (Case III) had a characteristic intra-aortic systolic pressure gradient.

Deformities of the aortic valve were present in six of the nine patients previously described; in four fusion of aortic cusps with the obstructing ridge or aortic wall occurred, while in the other two the aortic cusps were either thickened or thin and saccular. Abnormalities of coronary arteries (either origin in a blind pouch or obstruction of an orifice) were present in four of nine patients. In the present series, deformities of the aortic valve were present in each patient (in three the diagnosis was made on angiographic findings) and abnormalities of coronary filling were present in three of four patients.

Table I Supravalvular Aortic Stenosis; previously reported cases

Case No.	Author (s)	Age (yr.) and Sex	Blood Pressure (mm. Hg)	Clinical Findings	Poststenotic Dilatation	Catheterization Data	Surgery	Autopsy Findings
I	Mencarelli [1]	48, F			Absent	***		Normal heart size; circular narrowing producing circumscribed decrease it caliber of aortic wall just above attach ment of semi-lunar valves; obstruction contained fibrous tissue and elastifibers; normal aortic valves; mitra valvulitis
п	***	46, M	***		Absent		***	Cardiomegaly (650 gm.); rheumatic mitral stenosis; left ventricular hypertrophy; ring-like area of narrowing above free margin of aortic valves interwoven layer of elastic fibers and connective tissue at obstruction site no alterations of aortic valves or coronary ostia.
111	Cheu et al. [2]	30, M	210/60	Aortic stenosis; aortic insuffi- ciency; con- gestive failure	Present			Crescent-shaped fibrous membrane en- circling three-fourths of circumference of aortic lumen; central portion of membrane protruded 12 mm. into the lumen; lunulae of right and posterior aortic cusps were attached to the middle of the undersurface of the membrane; cardiomegaly severe; ascending aorta
IV	Burry [3]	37, F	150/125	Cardiomegaly; congestive failure; some features of Marfan syn- drome	Absent			distal to membrane greatly dilated Cardiomegaly with left ventricular hy- pertrophy; aorta grossly constricted at origin by two valvular ridges above aortic valves; aortic valve commissures fused with ridges; sinuses of Valsalva formed deep pouches, coronaries arose in pouches; myocardial fibrosis with mural thrombus; multiple arterial emboli
V	Kreel et al. [4]	12, M	95/45	Aortic stenosis; aortic insuffi- ciency	Absent		Died	above the sinus of Valsalva narrowing the lumen of the aorta, circumference of stenosing ring 3.8 cm., continuous with the aortic media; hypertrophy and fibrosis of ventricular myocardium; all aortic cusps thickened, right coronary cusp closely adherent to the aortic wall covering orifice of right coronary artery
VI	Denie and Ver- heugt [5]	25, M	· · · ·	Aortic stenosis; aortic insuffi- ciency	Absent	Significant lowering of diastolic pres- sure on track-back; left ventricular 150 mm. Hg; gra- dient 90 mm. Hg	Died	Circular narrowing at level of insertion of commissures, hypertrophy of plica normally forming margin of sinus of Valsalva; left coronary originated in blind pouch formed by fusion of free margin of left aortic cusp with aortic wall; poor filling of left coronary with barium; medial hypertrophy of aorta; fibrous myocarditis, left ventricle
VII	Morrow et al. [6]		Right arm 106/16 Left arm 112/0	Aortic stenosis	Absent	Peak systolic gradi- ent 52 mm. Hg; angiocardiogram		Shelf-like thickening at upper margin of sinuses of Valsalva, thickened aortic intimal plica at this level was point of insertion of fibrous bands originating at center of free edge of each leaflet; both ventricles hypertrophied
vin			Right arm 110/70 Left arm 90/60	Aortic stenosis	Absent	Angiocardiogram; peak systolic gra- dient 145 mm. Hg; tracing considered diagnostic	Died	(850 gm.); saccular aneurysm arising from ascending aorta near the origin of the innominate artery; coronary arteries enormously dilated; stenotic ridge above sinuses of Valsalva; aortic leaflets thin and saccular; healed dissecting aneurysm, arch of aorta; medial fibrosis of aorta
IX		7, M	94/70	Aortic stenosis	Absent	Peak systolic gradi- ent 60 mm. Hg	and tort	aorta small; coronary arteries enlarged uous; constriction distal to sinuses of ; sinuses of normal size; no surgical n attempted

Familial occurrence of this defect has not been previously noted. The familial history of the father in this family (six siblings died prior to three years of age) may have further genetic implications. Examination of the parents and three male siblings of two patients (Case III and IV) failed to disclose any cardiovascular abnormalities.

The marked differences in systolic pressure and pulses in the upper extremities in this series had good anatomic correlation with the angiographic studies; that is, in each case the smaller subclavian artery diameter corresponded with the side of the decreased blood pressure and pulse. This is probably a significant clinical finding.

There is unanimity of opinion that this defect, or combination of defects, is congenital and we would agree with this interpretation.

The obvious implications of this series, and of the previously recorded cases, are diagnostic and therapeutic. The obstruction *per se* may not be the only factor of consequence, particularly when the aortic cusps are malformed, the coronary ostia distorted or obstructed and aortic insufficiency a part of the clinical complex. Certain forms of the defect may not be amenable to complete surgical correction, and simple widening of the stenotic area may leave the patient with deformed aortic cusps, obstructed coronaries and marked aortic regurgitation.

From the diagnostic viewpoint, it would seem that all patients suspected of having an obstruction of the left ventricular outflow tract should undergo angiocardiographic studies, and an attempt at left ventricular and aortic pressure tracings should be made. Certainly it is mandatory that such diagnostic studies should be made in patients, particularly males, with evidence of obstruction of left ventricular outflow tract in the absence of poststenotic dilatation of the aorta, and with systolic pressure and pulse differences in the arms, before they are subjected to surgery. At the present time there is no objective evidence that this particular lesion is surgically correctable in toto or that partial relief of the obstructing ridge will be accompanied by increased longevity.

SUMMARY

The clinical findings in four patients with supravalvular aortic stenosis are described, and previously reported cases reviewed.

The association of this defect with the clinical

findings of aortic stenosis, a marked difference in the blood pressures and pulses in the upper extremities, and the frequent absence of poststenotic dilatation of the aorta is stressed. The frequency with which one or a combination of the following defects occur, namely, aortic valve deformity, aortic regurgitation and abnormalities of coronary artery filling, is noted.

The present study provides documentation of the familial occurrence of this defect, or combination of defects.

Angiocardiographic studies are necessary to confirm the diagnosis. Complete surgical correction may not be possible, and there is no objective evidence available at present that partial correction will be accompanied by increased longevity.

ADDENDUM

Since preparation of this manuscript several interesting studies of supravalvular aortic stenosis have appeared.

Perou [8] presented pathologic data from two patients with supravalvular aortic stenosis. Both patients were males. Poststenotic dilatation of the aorta was not present and valvular involvement with distortion of the coronary orifices was present in one patient.

The author also attempted a morphologic classification of this entity, with the reservation that future reports would undoubtedly include intermediate conditions. The classification: (1) true supravalvular aortic stenosis or coarctation, (2) obstructing and stenosing supravalvular aortic membrane (e.g., the case of Cheu et al. [2]), and (3) non-stenosing or non-obstructing supravalvular aortic membrane, band or cord.

McGoon and his associates [9] reported surgical experiences in three patients with supravalvular aortic stenosis. Two of the three patients were boys. A marked difference in pulses in the upper extremities was noted in the one girl. The three patients were operated upon; no apparent abnormalities of the aortic valves were noted, and relief of the stenosis and survival of the patients was reported.

Dotter and his associates [10] performed selective angiocardiographic studies on three patients with supravalvular aortic stenosis. Surgery was deferred in one patient, and accompanied by an excellent result in the second. The third patient did not survive the surgical procedure.

From a series of 125 patients with isolated

aortic stenosis, Hancock [11] discussed one boy with supravalvular stenosis. There was a marked arterial pulsation in the right side of the neck and a supravalvular pressure gradient was demonstrated; the diagnosis was confirmed by aortography. Partial resection of the defect was performed.

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Cardiac Malformation in Mongolism*

A Prospective Study of 184 Mongoloid Children

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DEBATE concerning the nature and frequency of cardiac malformation in mongolism continues. Most studies on this subject have not succeeded in answering the question completely chiefly because of the selection of patient material.

Since the newer technics in physical and accessory examinations now permit more certain classification of congenital heart disease, we have attempted to study heart malformation in mongolism by examining the entire mongoloid population attending the Hospital for Sick Children, Toronto, in a recent two-year period. The unusual size of this group is due to the availability to family physicians and paediatricians of a confirmatory dermatoglyphic test for mongolism [1]. A preliminary report of the first year of the study [2] and data on physiologic studies obtained from mongoloid subjects with normal cardiovascular systems early in the study [3,4] have already been published. This paper concerns itself with the details of the sample, methods employed in diagnosis and the late results in the study. Data of genetic interest are presented only in brief.

MATERIAL AND METHODS

The mongoloid infants and children studied were referred to the Hospital for Sick Children between July 1955 and June 1957. The final analysis of data was made after the close of the investigation in December 1959.

Genetic Studies. Because of the widespread use made of the diagnostic service, many patients with minor signs of mongolism such as a simian crease, short fifth finger or slanted eyes, were referred by alert physicians. Approximately two-thirds of those referred during this two-year period were excluded as definitely non-mongoloid. The one patient in whom there

was doubt about diagnosis was also excluded. A total of 184 mongoloid subjects who were carefully screened with clinical and dermatoglyphic examinations were included in this study. The group included fifty-seven newborn infants, fifty infants aged between one and six months; seventeen infants aged seven to twelve months, and sixty children over one year of age. Only seventeen of the latter group were between five and fifteen years of age. Of these children, 110 came from Metropolitan Toronto, twenty-eight were from towns or cities within a 50 mile radius of Toronto, fourteen came from Northern Ontario and thirty-two from Southern Ontario outside of the 50 mile radius of Toronto. The reasons for referral are given in Table I.

When the parents accompanied the patient, detailed family histories were obtained for genetic evaluation, and counselling services were rendered upon request. Histories were obtained from 142 families at the time of the original contact or during subsequent visits.

After a definite diagnosis of mongolism had been made, the patient was referred to the Cardiac Service for heart assessment. This procedure was reversed in

Table 1
REASON FOR REFERRAL TO THE HOSPITAL FOR SICK
CHILDREN, TORONTO, OF 184 MONGOLOID SUBJECTS
EXAMINED IN A TWO-YEAR PERIOD, 1955–1957.

Reason for Referral	No. of Patients
Medical or genetic counselling	123
Congenital heart disease	4
Autopsy	6
Other (none directly related to mongolism or congenital heart disease) e.g., infection,	
other malformation and tonsillectomy	51
Total	184

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only four patients who were first referred for cardiac examination.

Cardiac Studies. Six patients were first seen at autopsy. In all other mongoloid subjects in the series minimum study consisted of a physical examination, and procurement of a 6 foot roentgenogram of the chest, and a standard twelve lead electrocardiogram. Fluoroscopy with barium swallow was performed in 142 of the group.

Additionally, cardiac catheterization, requested for all subjects, was eventually performed in fifty-five; fourteen underwent angiocardiography. All patients were assessed by a paediatric cardiologist and in 180 the examination was made by one person (R. D. R.).

Early in the study it became apparent that factors, such as the duration of transitional pulmonary circulation of newborn infants, so seriously masked the physical signs of septal defects as to preclude the diagnosis of a normal cardiovascular system in mongoloid subjects during the neonatal period by simple physical examination alone. Consequently no firm opinion was expressed on normal cardiac status in this age period unless autopsy proof or catheter study indicated distinct normality, or results of subsequent physical examination with supportive electrocardiographic and roentgenographic evidence were within normal limits.

When the initial examination failed to produce a satisfactory conclusion about the cardiovascular status and when additional investigations of cardiac catheterization and angiocardiography were refused by either the parents or the family physician, repeated physical examinations coupled with electrocardiograms and chest roentgenograms were carried out during the follow-up period in an effort to clarify the state of the heart. Due to the wide dispersal of the subjects and to deaths in the group, it was not possible to reassess all subjects, nevertheless in only ten of the 184 subjects did the cardiovascular status finally have to be classified as "uncertain."

RESULTS

Among the 142 families whose detailed histories are known, there were ten with a second case of mongolism: four patients had mongoloid sibs, one had an affected uncle and five had affected cousins. All these cases have been verified either by an institution, a family physician or personally. Transmission of the abnormality was just as frequent through the male line as the female. There were two instances of consanguinity: in one there was a second retarded child and the parents were first cousins once-removed, and in the other the parents were third cousins. In neither instance was there a repetition of mongolism.

In two families there were sibs with congenital

TABLE II
THE CARDIAC STATUS AT THE END OF 1959 IN 184
MONGOLOID CHILDREN INITIALLY SEEN BETWEEN

Classification	No. of Patients
Normal	. 104
Malformation	. 70
Uncertain	. 10
Total	184

JULY 1955 AND JUNE 1957

heart disease. In both cases the mongoloid patients had cardiac malformations. However, in the families with a repetition of mongolism there did not appear to be any association between mongolism and congenital heart disease.

The mean maternal age for 181 patients is 33.5 years. If the upper limit for young mothers is fixed at this mean, then in all four families with two mongoloid sibs, the first and two of the second mongoloid sibs were born to young mothers. The mean maternal age for these eight patients was 29.9 years. Only 9 per cent of seventy pregnancies occurring after the birth of a mongoloid child among young mothers ended in abortions, stillbirths or neonatal deaths, whereas among older mothers the frequency was 29 per cent of forty-two pregnancies; there was no difference between young and older mothers in the frequencies of early deaths among premongoloid pregnancies (22 per cent for both). In the analysis of the dermal patterns of the fingers, palms and soles [1], the mean index for mongoloid subjects with congenital heart disease was 5.03 and for those with normal hearts 4.07.

The final classification of the cardiac status in 184 mongoloid subjects is shown in Table II.

Normal Cardiovascular Status. In these subjects the initial or subsequent cardiac examinations revealed normal physical signs. Particular attention was paid to the colour on crying, splitting of the second heart sound, analysis of heart murmurs and the appearance of the electrocardiogram and roentgenogram. In sixteen of the 104 subjects, cardiac catheterization was normal. As previously mentioned, especially stringent criteria were used for the diagnosis of a normal heart in the newborn period.

Uncertain Cardiac Status. Of ten subjects with this final designation, five were not re-examined after the initial clinical examination in the new-

NATURE AND FREQUENCY OF THE INDIVIDUAL CARDIAC MALFORMATIONS FOUND IN SEVENTY OF 174 MONGOLOID SUBJECTS

Defects	No.	%
Atrioventricular canal defects		
Atrioventricularis communis 22 Ostium primum	25	36
Ventricular septal defect	23	33
Patent ductus arteriosus	7	10
Secundum atrial septal defect	6	9
Isolated aberrant subclavian artery	5*	7
Tetralogy of Fallot	1	1
Simple pulmonary stenosis	1	1
Equivocal type	2	3
Totals	70	100

^{*} This proportion could be slightly low as it represents a specific examination in only ninety-two mongoloid subjects of a possible 109 with otherwise normal hearts. Two other subjects with aberrant subclavian arteries were classified with their major intracardiac defect.

born period although known to be still alive at final follow-up. The other five had equivocal cardiac abnormality by virtue of an equivocally abnormal electrocardiogram and/or chest roent-genogram even after a second or third examination several weeks to one year later. In none of the ten subjects was permission for cardiac catheterization obtained. In three patients in whom venous angiocardiography was permitted as an alternative during the first week of life, the cardiac status was not clarified.

Cardiac Malformation. Seventy (40 per cent) of the 174 subjects in whom cardiac status is known were found to have congenital abnormalities of the cardiovascular system. The distribution of defects is shown in Table III.

Atrioventricular canal defects: All mongoloid subjects included in this category had an electro-cardiogram whose frontal vector was oriented in a counterclockwise direction with the main portion of the loop above the horizontal axis. The axis of QRS in these tracings was never less than minus 70 degrees. Separation between the complete (atrioventricularis communis) and incomplete (persistent ostium primum) forms posed problems but was made in the following manner.

At autopsy in eight subjects, the diagnosis was confirmed as atrioventricularis communis. No example of isolated persistent ostium primum

was found at postmortem examination. Cardiac catheterization permitted six subjects to be classified as having atrioventricularis communis since in five both an atrial and ventricular defect were probed by the catheter tip and the rise in blood oxygen saturation commenced at the atrial level. In one more, only the ventricular component of this defect was probed, but the rise in oxygen saturation started at the atrial level. Three patients (all acyanotic clinically) were found at catheterization to have a rise in blood oxygen saturation at the right atrial level, an atrial defect by probing, and in two an intact ventricular septum following left ventricular injection of contrast material. These three patients were classified as having persistent ostium primum defects alone.

Eight subjects in whom a variety of auscultatory signs were found depending upon the age, state of the pulmonary vascular resistance and the degree of atrioventricular regurgitation, and in whom distinct central cyanosis of greater or less degree was noted, were diagnosed atrioventricularis communis. There were no examples of true isolated persistent ostimum primum in the purely clinical group.

Ventricular septal defects: Autopsy confirmation of this diagnosis was obtained in five patients. The detection of a significant left-to-right shunt at ventricular level at cardiac catheterization confirmed the presence of the defect in thirteen others. In six of these, the defect was probed by the catheter tip; in two others a left ventricular cineangiocardiogram provided additional evidence of the site of the shunt. In five patients the classic physical signs of a moderate-sized or large ventricular septal defect with normal pulmonary vascular resistance were supported by electrocardiographic and roentgenologic evidence. In none of this clinical group was the mean axis QRS in the electrocardiogram less than 0 degrees.

Patent ductus arteriosus: The autopsy of one subject at six months, in whom a loud continuous murmur with cardiac enlargement and left ventricular hypertrophy had been present during life, showed an isolated patent ductus arteriosus. Cardiac catheterization, with a rise in oxygen saturation of pulmonary arterial samples together with passage of the catheter through the ductus arteriosus, established the diagnosis in two other children. There were four others, all acyanotic, in whom a loud continuous murmur and compatible electrocardiographic and roent-

TABLE IV
ASSOCIATED ANOMALIES AND CARDIAC STATUS IN
THIRTY-ONE MONGOLOID SUBJECTS

Associated Anomaly	Total (no.)	Cardiac Malformation (no.)		
Gastrointestinal Harelip	2	6*		
Tracheoesophageal fistula	3			
Diaphragmatic hernia	1			
Oesophageal hiatus hernia (gross)				
Duodenal atresia	i			
Umbilical hernia	3			
Inguinal hernia	1			
Imperforate anus	48			
Reduplication	1	1		
Skeletal	7	4		
Syndactyly	4.			
Polydactyly	1			
Talipes	1			
Spina bifida occulta	1			
Ocular	6	3*		
Strabismus	2			
Cataract	2	0		
Cerebral palsy	10	0		
Arnold-Chiari malformation	1			
Pulmonary	1	0		
Agenesis lung	1			
Total	33 (31 patients)	13 (12 patients)		

Note: The asterisk signifies one patient with two anomalies and heart disease while the closed circle implies one patient with two anomalies and a normal heart. The triangle represents one patient with equivocal cardiac status.

genographic evidence satisfied the diagnostic criteria for this malformation.*

Secundum atrial defects: This defect was confirmed at autopsy in two patients and in two others after cardiac catheterization by having a rise in oxygen saturation in the right atrium, minimal interatrial pressure gradient with probing of the defect and normal pulmonary arterial pressures. Both had electrocardiograms with a clockwise frontal vector and a right ventricular diastolic overloading pattern. Two other patients classified earlier as "equivocal" were found at the age of four and a half and seven years, respectively, to have a blowing, ejection, systolic murmur in the pulmonary area, a wide fixed splitting of the second heart sound and an apical, mid-diastolic murmur with a compatible roentgenologic picture and a clockwise vector in the electrocardiogram.

Isolated aberrant subclavian arteries: The diagnosis of this lesion was made with barium in the

* Four additional patients with ventricular septal defect and two with secundum atrial defects are known to have had associated patent ductus arteriosus, but were classified according to their major defect, and are included in the totals under the appropriate major malformation.

Table v
CARDIAC STATUS AT AUTOPSY IN TWENTY-NINE
MONGOLOID SUBJECTS

Cardiac Status	No. of Patients		
Normal heart	2		

oesophagus at routine fluoroscopic examination of the heart in five subjects. No evidence of other cardiovascular lesion was revealed in these and in two, this finding was confirmed by normal cardiac catheterization.

Tetralogy of Fallot: The one patient with this malformation was first seen at three days of age; he died at three months. Autopsy examination confirmed the previous clinical diagnosis of tetralogy of Fallot with pulmonary atresia.

Isolated pulmonary valve stenosis: One patient, first seen at the age of eight months and reassessed at two years, had evidence of mild pulmonary valve obstruction, namely, an organic, systolic murmur of ejection type in the pulmonary area without thrill and with a normal second heart sound. The heart size was normal but the roent-genogram showed a distinct pulmonary artery segment bulge. Barium swallow and lung vascular markings were within normal limits. The electrocardiogram was normal.

Equivocal type: Two patients were classified in this group, neither having been investigated by cardiac catheterization. Both had convincing signs of congenital heart disease.

One girl, two and a half months of age, was referred because of failure to thrive and was found to have congenital heart disease at the outpatient examination. She was a fairly well nourished, acyanotic mongoloid infant with no evidence of congestive heart failure. There was a faint thrill, with a grade 2 early systolic murmur at the third and fourth left intercostal space, no mitral radiation. No diastolic murmur was heard. The second heart sound was accentuated and closely split. The femoral pulses were palpable; the blood pressure was 80/45 mm. Hg. The cardiothoracic ratio at the time a roentgenogram was taken was 7:11.5. There was a very marked pulmonary artery bulge and some enlargement of the

Table VI

AGE AT DEATH AND RELATIONSHIP TO SPECIFIC CARDIAC STATUS IN FIFTY-THREE MONGOLOID SUBJECTS

Age at Death	Nature of Cardiac Lesion									
	Atrioventricular Canal	Ventricular Septal Defect	Patent Ductus Arteriosus	Atrial Septal Defect	Tetralogy of Fallot	Equivocal	Norma			
Newborn period	2	3	0*	0	0	0	9			
2-6 mo	5	3	0	1	1	0	3			
7–12 mo	4	3	2	0	0	0	1			
>1 yr	4	2	1	1	0	0	5			
Age unknown	0	0	0	0	0	1	2			
Total	15	11	3	2	1	1	20			

^{*} Wide anatomic patency in the first week and probe patency thereafter were accepted as normal in this period.

right atrium present. The lung vascularity was slightly increased and the peripheral lung vascular markings were reduced. Barium swallow showed no abnormalities. The electrocardiogram revealed combined ventricular hypertrophy with a counterclockwise vector around the horizontal axis.

The second patient was seen at the age of eighteen months at the time of admission to the hospital with a viral illness. While pink at rest, there was slight cyanosis on crying. No thrills were noted. There was a loud, pulmonary ejection click, a short, ejection systolic murmur, and a greatly accentuated and narrowly split second heart sound. The apex beat was

right ventricular in character and there was a distinct precordial bulge. The femoral pulses were palpable. The cardiothoracic ratio was 7.9:13.9 with increased lung vascular markings. The electrocardiogram showed marked right axis deviation (plus 180 degrees) and a figure of 8 loop along the horizontal axis.

The evidence in these patients was acceptable, therefore, as indicating congenital heart disease, but the exact nature of their defects was not sufficiently established to allow certain categorization into a particular group.

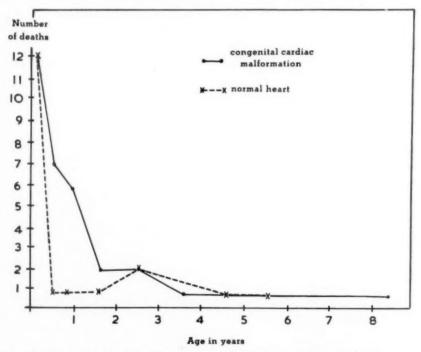


Fig. 1. The age at death in fifty-one mongoloid subjects related to the presence or absence of congenital cardiac malformation.

TABLE VII

THE MODE OF DEATH IN FIFTY-TWO MONGOLOID SUBJECTS IN WHOM THE CARDIAC STATUS WAS KNOWN

	Mode of Death							
Cardiac Status	Other Malfor- mation	Infec- tion	Heart Failure	Failure and Infection	Respiratory Distress Syndrome	Sudden Death	Other	Unknown
Normal	7 0	3 9	0 3	0 2	2 1	0 2	2 0	6 15
Total	7	12	3	2	3	2	2	21

Associated malformations: It is conceded as unlikely that an exact accounting of the associated malformations was obtained in this study, but obvious major internal and easily distinguished external malformations were found in thirty-one patients, two of whom had two abnormalities. The type of additional defect is shown in Table IV.

Deaths: By the end of this study fifty-three patients had died. Twenty-seven of these were female and twenty-six male. Of the group, thirty-two had congenital heart disease, twenty had a normal heart and one had equivocal heart disease. Because not all the patients were followed up for the same period of time, it is not possible to estimate the proportion of the whole group which this figure represents. Autopsy examination was obtained in twenty-nine patients, the cardiac status in these being shown in Table v. The relationship between age at the time of death and the specific and non-specific cardiac status is shown in Table vi and Figure 1.

Information on the mode of death is incomplete (Table VII) mainly because over one-third of the patients died at home or in boarding establishments. Although most of these deaths were probably due to infection, it is difficult to be sure of this point when many had serious congenital heart disease. One death from leukemia and one accidental death are included in the table.

COMMENTS

This study finds cardiovascular anomalies in 40 per cent of a group of 174 mongoloid children. Recent reviews of the literature [2,5] emphasize the varying frequency of congenital heart disease in mongoloid subjects in previous studies. Since series containing small numbers of cases are un-

likely to contribute meaningfully to establishing the frequency of congenital heart disease in mongoloid subjects, an important requirement is that a substantial number of subjects be included in any new study. It is of major importance that, within the limits of practicability, the subjects be as free as possible from selection. In all major studies it has been generally agreed that cardiac defects in mongoloid subjects are much more commonly seen in younger than in older subjects [5-7], a tendency noted in the present series. (Fig. 2.) A prime consideration, therefore, is to avoid a concentration of patients beyond infancy. It is for this reason that institutions for mental retardation are an unsatisfactory source for procurement of frequency figures. Yet children's hospitals are not usually the best source of patient material, there being a tendency for the acutely ill patient, or those with congenital heart disease to be seen more often than the well mongoloid subject in such surroundings. Except for the last two-month period when ten of sixteen mongoloid subjects were found to have congenital heart disease, the proportion with cardiac malformation in any two-month period of the study was relatively uniform. It has been inferred that autopsy examination of a large group of mongoloid subjects will dilute this bias and provide a more accurate indication of the incidence of congenital heart disease. In a recent important study [5], seventy-nine of 141 (56 per cent) mongoloid subjects were found to have congenital heart disease at autopsy. Unfortunately, a higher proportion of mongoloid subjects with congenital heart disease tend to come to autopsy in most hospitals. A similarly high proportion with cardiac malformation, 59 per cent (seventeen of twenty-nine), would be found in the

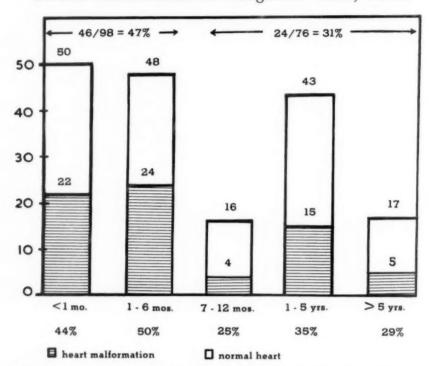


Fig. 2. The age at first examination and relation to congenital cardiac malformation in 174 mongoloid subjects whose cardiac status is known.

present study if attention were confined to autopsy material alone. As a corollary, in twenty-four subjects of the present study in whom no autopsy was performed, heart malformation was found in only 33 per cent. It is the inclusion of the subjects not necessarily ill, with no reason for entering a hospital, which reduces the proportion with congenital heart disease to 40 per cent in this series as a whole.

Ideally, the frequency of congenital heart disease in mongoloid subjects should be obtained from a prospective study of a large nursery population with inspection of all patients by a trained team, dermatoglyphic and chromosomal analyses of doubtful cases, and cardiovascular examination by competent personnel, 100 per cent autopsy permission and complete follow up of all mongoloid subjects for a long period of time with full cardiovascular work-up at some stage in all cases. It is unlikely that a study of this sort could ever be accomplished. The present investigation, while not free of selective elements, aims at compromise. It particularly avoids the bias due to the diminishing proportion of mongoloid subjects with congenital heart disease at older ages by concentrating heavily on the infant age group. In the two-year period concerned, of 110 mongoloid infants and children from Metropolitan Toronto, eighty-one were

under the age of one year when first seen. Knowing the number of live births in the area during the period, we may reasonably infer that almost every mongoloid baby born in Toronto was seen in the study. By including carefully studied living patients, the tendency to higher proportions with congenital heart disease seen in an autopsy series is lessened. By virtue of a large sample, mostly referred for medical counselling and seen during a short period of time by the same observers, the need to rely on multiplicity of examiners or past records was obviated and the resultant confusion in criteria for diagnosis avoided.

A second debatable point is the type of cardiac lesion found in mongolism. Although atrioventricularis communis has attracted most attention, several authors have suggested that isolated ventricular septal defect also is a frequent malformation [2,7-9]. More recently it has been suggested that, while some cardiac lesions are less commonly seen in mongoloid subjects, the major bulk of malformations occur in roughly the same incidence as in nonmongoloid subjects with congenital heart disease [5]. Ventricular septal defect is certainly a leading malformation in both mongoloid and non-mongoloid subjects, but in our series atrioventricularis communis forms a much

higher proportion of cardiac malformation in mongoloid subjects than in non-mongoloid subjects in the same institution [2,10]. Apart from this strikingly high frequency of atrioventricularis communis and the rarity of transposition of the great vessels, coarctation of the aorta and aortic stenosis, the order of frequency of the other defects is, in our series, not greatly different from the common experience in large series of congenital heart disease. One anomaly, originally noted to be common in mongolism by Strauss [11] and since by others [7], is isolated aberrant subclavian artery. In 1,000 normal subjects examined at autopsy [12] this malformation occurred in 1.3 per cent whereas in the present series it occurred in 5.6 per cent of mongoloid subjects. The detection of these cases was due to the use of barium examination at fluoroscopy. It is understandable that the anomaly might be overlooked at autopsy or on simple clinical examination when the heart is structurally normal otherwise.

When additional congenital malformations were found, they were no more frequent in patients with congenital heart disease (17 per cent) than in those with normal hearts (18 per cent); findings similar to those of other workers [5]. We have previously shown [2] that many of the neonatal deaths in mongolism are due to gross gastrointestinal anomalies. The serious implication carried by a diagnosis of mongolism is emphasized by the fact that fifty-three deaths occurred in the study group, all but six died during infancy. As might be expected, the distribution curve of deaths in those with heart defects is similar to that in any subjects with congenital cardiac malformations. From a relatively high number in the first three months, the number gradually falls during the next six months. Two-thirds of the mongoloid subjects who died in this study during the first year of life had congenital heart disease. By comparison, those mongoloid subjects free of significant cardiac malformation have their highest death rate in the first month, after which time the proportion diminishes rapidly to a low figure. These results support the view commonly held that significant congenital heart disease in mongoloid infants carries a grave prognosis. They emphasize both the need for an accurate cardiac assessment of such patients and for caution in firmly excluding cardiac malformation on the basis of a clinical examination alone in the neonatal period.

The mean maternal age of 33.5 years in our series is lower than the means reported by other authors [13], which average about 37 years. It is difficult to say whether this is a peculiarity of the sample or an indication of a real trend toward younger maternal ages in recent years, either because of an increase in births among younger mothers in the general population or because of changing environmental conditions that might induce non-disjunction at random. The frequency distribution for maternal ages is different from that reported by Penrose [14] (Fig. 3); the difference between the means is highly significant. There is a slight but insignificant increase in the mean maternal age of mongoloid subjects with heart disease.

The tendency for mongolism to repeat in younger mothers suggests that they are better able to carry affected children to term; older mothers may be inclined to have more severely affected and therefore inviable offspring as suggested by the frequency of miscarriages, stillbirths and neonatal deaths, although it must be borne in mind that abortions are known to increase with maternal age [15]. Within our series there appeared to be a tendency for older mothers to have more severely affected children: 70 per cent of forty congenitally deformed mongoloid subjects who died were born to older mothers. The deformities were mainly serious septal defects and severe malformations of the gastrointestinal tract. The mean maternal age for this group was 34.8 years. However in the over-all picture there is an inconsistency when our results are compared with those of Penrose [14] whose sample consists mainly of older children with a much higher mean maternal

Among the several dermatoglyphic configurations, one important diagnostic pattern is the position of the axial triradius of the palm. In the majority of mongoloid imbeciles the triradius is found in the center of the palm whereas in normal subjects it is usually found closer to the wrist or in a "low" position. In mongoloid subjects with normal hearts 27.5 per cent had at least one low triradius, compared with 28.5 per cent of those with abnormal hearts. If those with isolated right subclavian arteries are not classified as having a heart malformation only 24 per cent of mongoloid subjects with heart defects have a low triradius compared with 40 per cent of those with normal hearts. This difference is significant (P < 0.05). The presence

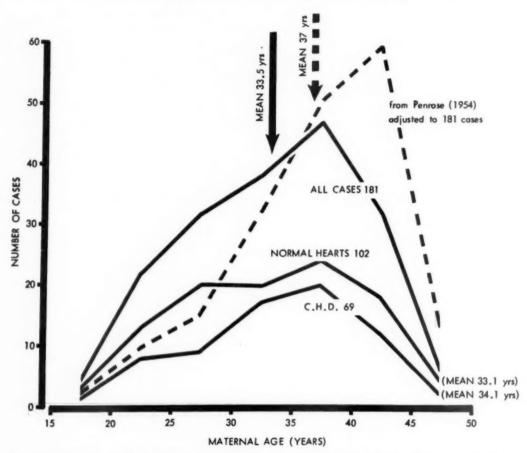


Fig. 3. Maternal age distribution of 181 mongoloid children according to cardiac status and compared with the distribution reported by Penrose [14].

or absence of other anomalies was irrelevant. The significance of these results is being tested by analysis of the dermal patterns of non-mongoloid subjects with heart malformations.

With the recent discovery of trisomy in man it is interesting to speculate upon the association between the extra chromosome and congenital heart disease. Trisomy in mongolism has now been well established. Two other trisomy syndromes have also been discovered [16–18]. One syndrome is characterized by cleft lip and palate, polydactyly, mental retardation and a ventricular septal defect; the other includes micrognathia, low set ears, hernias, mental retardation and a ventricular septal defect. Mental retardation and a cardiac malformation, usually a septal defect, are associated with all three autosomal trisomy syndromes.

Evidently certain normal genes can disrupt development when found in triplicate. No doubt large numbers of genes are involved in intelligence and in heart formation and these may be presumed to be distributed over many chromosomes. Therefore, it is not surprising that mental deficiency is present in all three autosomal trisomy syndromes. On the other hand, since congenital heart disease, although common, is not a constant feature of trisomy, a question of lowered penetrance may be involved, or it is not improbable that the malformation might be the secondary result of a basic developmental disturbance depending upon the timing of that disturbance.

SUMMARY

One hundred and eighty-four mongoloid infants and children (mainly referred for counselling) have been examined at the Hospital for Sick Children, Toronto, over a recent two-year period. Practically all mongoloid babies born during this time in Toronto were included in the sample and only seventeen of the group were older than four years.

All subjects were seen in turn by a geneticist and a paediatric cardiologist, and follow-up in some cases was as long as four and a half years.

As complete a cardiac study as was permitted was made. In almost a third of the group this examination was followed by cardiac catheterization.

Of 174 subjects in whom a definite statement about the cardiac status could be made, seventy (40 per cent) had congenital heart disease. The leading malformations were atrioventricularis communis and ventricular septal defect; less common were patent ductus arteriosus, atrial septal defect and isolated aberrant subclavian artery. Additional congenital deformities of other systems were found in thirty-one subjects (17 per cent). Fifty-three of the group died during the next four and a half years. Of these, thirty-two had congenital heart disease.

The problems of estimating the frequency and type of congenital heart malformation in mongolism are discussed and the importance for prognosis of recognizing such malformation early in life is emphasized.

A low axial triradius in the palmar dermal pattern of mongoloid subjects with significant heart malformation was found less frequently than in those with normal hearts.

Differences between the affected and subsequent offsprings of mothers younger or older than the mean maternal age of the group are shown. The possible nature of the relationship between trisomy and congenital heart disease is discussed.

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Renal Pathology in Paroxysmal Nocturnal Hemoglobinuria*

An Electron Microscopic Illustration of the Formation and Disposition of Ferritin in the Nephron

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The disease now called paroxysmal nocturnal hemoglobinuria was characterized in a case report by Marchiafava [1] in 1931 as "hemolytic anemia with perpetual hemosiderinuria." At autopsy a heavy deposition of iron-containing pigment was found in the proximal convoluted tubules of the kidney. Herein reported are two cases of this rare disease in which kidney tissue was examined at autopsy in the first case and after renal biopsy in the second. A study of renal tissue from the second case, with the electron microscope, demonstrated the sites of ferritin formation in the nephron and two modes of removal of ferritin from the nephron.

METHODS

Percutaneous biopsy was performed using the method of Kark and Muehrcke [2]. The specimens for light microscopy were fixed in 10 per cent buffered formalin for three hours, dehydrated in graded alcohols and embedded in paraffin (M.P. 50 to 55 degrees). Sections were cut at 2μ and stained with hematoxylin and eosin, periodic acid-Schiff, Gomori's trichome and Prussian blue for iron.

For electron microscopy a 1 mm. segment of the cortical end of each biopsy cylinder was removed immediately and processed. This tissue was fixed in 2 per cent OsO₄ in veronal-acetate buffer, pH 7.6, to which 0.41 gm. of sucrose and 1.5 mg. of calcium chloride were added per 5 cc. of fixative. After fixation the tissue was rinsed five minutes in buffer, dehydrated in five minute changes of successive 10 per cent grades of methanol (beginning with 10 per cent), and embedded in prepolymerized (2 per cent lucidolbenzoyl peroxide) 3:7 mixture of methyl and n-butyl methacrylates by completion of polymerization at 60 to 65°c. Sections were cut with glass knives on a

Servall Porter-Blum microtome on to 50 per cent acetone, mounted on collodion-coated slit grids, sandwiched with another layer of collodion and examined at 60, 80 or 100 kv. in a Philips EM100A electron microscope fitted with a 30 μ objective aperture. Micrographs were made on Kodak Contrast Lantern Slide Plates at initial magnifications of 2,000 to 30,000 \times at exposures of one to four seconds and were photographically enlarged up to five times.

The following nomenclature is used to refer to the iron particles described.

Hemosiderin: Golden brown granules, visible on light microscopy (H, Fig. 3), which stain bright blue with the Prussian blue stain for iron. (H, Fig. 1 and 2.) These are visible on electron microscopy as relatively large non-membrane-limited clumps of osmophilic material. (H, Fig. 6.)

Siderosome: Membrane-limited accumulations of osmophilic material visible on electron microscopy (S, Fig. 6) and indistinguishable from the structures given this name by Richter [3] and described in animals after intravenous injection of hemoglobin.

Ferritin: Electron dense particles 50 to 60 Å in size and visible on electron microscopy. These may appear as individual particles (F, Fig. 5 and 7) or in siderosomes or in hemosiderin granules.

Iron micelle: The sub-units (arrows, Fig. 4) of ferritin visible on electron microscopy with 15 Å resolution as individual 15 to 20 Å size particles [4].

CASE REPORTS AND PATHOLOGIC DESCRIPTIONS

CASE I. A forty-nine year old white man (T. P., C.G.H. No. 1326) died at home on December 30, 1957, after an acute episode of chest pain and dyspnea. He had been ill since the age of thirty-one (1939) with hemolytic anemia. Hemoglobinuria had been noted intermittently since that time in specimens voided in the morning. During the subsequent eighteen years he

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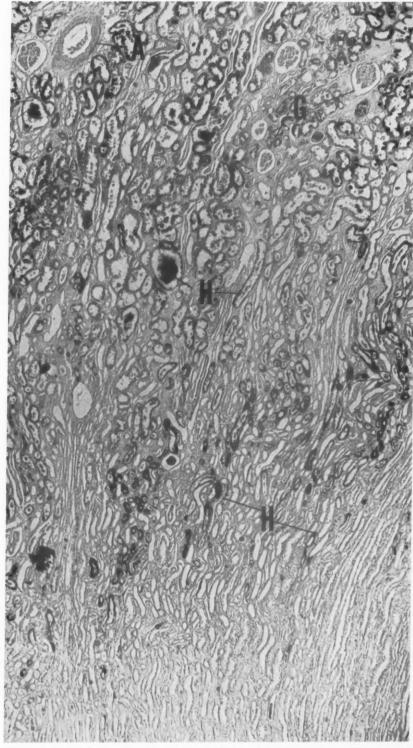


Fig. 1. Case i. Photomicrograph of kidney section stained with Prussian blue for iron. The transition (lower H) from cortex (above) to medulla (below) is marked by the relative density of hemosiderin (H) which is abundant in the cortex and sparse in the medulla. Clumps of hemosiderin granules (H) are present in tubular epithelium and in tubule lumina. Hemosiderin is not present in arteries (A) or glomeruli (G). Magnification \times 40.

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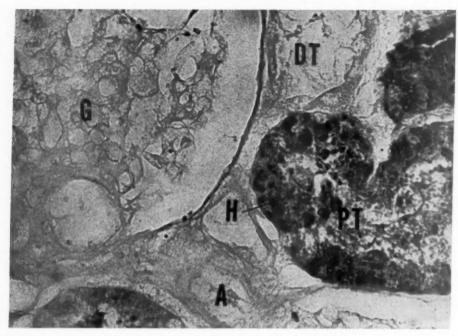


Fig. 2. Case II. Photomicrograph of kidney section stained with Prussian blue for iron. Hemosiderin granules (H) appear as dark masses in epithelial cells and lumen of a proximal tubule (PT). Very little hemosiderin is present in the glomerulus (G), arteriole (A) or distal tubule (DT). Original magnification \times 660.

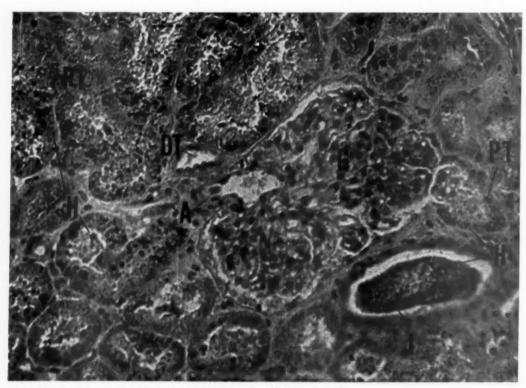


Fig. 3. Case II. Photomicrograph of kidney section stained with hematoxylin and eosin. Hemosiderin granules (H) are abundant in proximal tubule (PT) epithelial cells and lumina. Hemosiderin is not present in epithelial cells of a distal tubule (DT) but there is a large hemosiderin-containing cast (J) in a distal tubule. No hemosiderin is present in an arteriole (A). Some hemosiderin may be present in a glomerulus (G). Original magnification × 320.

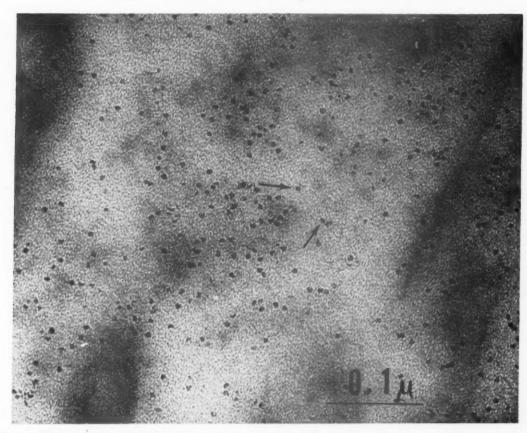


Fig. 4. Case II. Electronmicrograph of proximal convoluted tubule cell cytoplasm. Ferritin particles under high magnification are demonstrated to be made up of 15 to 20 $\mathring{\rm A}$ sub-units (iron micelles) which are 15 to 20 $\mathring{\rm A}$ apart. The iron micelles are especially well demonstrated in two of the ferritin particles designated by arrows. Bar at lower right indicates 0.1 μ . Magnification \times 240,000.

had had, in addition to several admissions to other hospitals, fifty-three admissions to this hospital. During these eighteen years he had received over 300 blood transfusions. His course was characterized by episodes of thrombophlebitis, pneumonia, pulmonary infarcts, cystitis, jaundice and transfusion reactions in addition to symptoms and signs of severe anemia. In June 1944 the diagnosis of paroxysmal nocturnal hemoglobinuria was established by a positive reaction to the Ham test [5]. This test was repeated in 1948, 1954 and May 1957 with the same positive result. Hemosiderinuria was demonstrated on many occasions. Blood non-protein nitrogen one month before his death was 26 mg. per cent, unchanged from the non-protein nitrogen in March 1943 of 28 mg. per cent. In 1952* the plasma cholinesterase was 0.52 delta pH units and the erythrocyte cholinesterase was 0.18 delta pH units.

At necropsy the heart (740 gm.) showed both right (7 mm.) and left (15 mm.) ventricular hypertrophy. The coronary arteries contained some intimal plaques

* These measurements were made in the laboratory of Dr. Joseph H. Holmes. Normal values in this laboratory are plasma 0.6 to 1.1 delta pH units, erythrocytes 0.7 to 1.2 delta pH units.

but were widely patent. The lungs (right 510 gm. and left 410 gm.) appeared normal, the pleura was thickened by fibrous connective tissue. The capsule of the spleen (400 gm.) was thickened and adherent to the diaphragm. The liver weighed 2,160 gm. The surface of the kidneys (right 245 gm. and left 280 gm.) was red-brown and slightly granular. Prussian blue stain for iron revealed abundant iron in the cortex (7 mm.) and little in the medulla (18 mm.). The bone marrow was abundant and red. The remainder of the examination including the examination of the brain was non-contributory.

On microscopic examination the lungs showed slight emphysema and atelectasis, and recanalized thrombi in many of the small pulmonary arteries. In the liver there was slight fatty metamorphosis of central hepatic cells, without fibrosis. The spleen exhibited evidence of congestive splenomegaly. Bone marrow showed erythroid hyperplasia. Prussian blue stain for iron failed to reveal iron in the bone marrow or spleen and only a sprinkling of iron in a few hepatic cells. In the kidneys the arteries (A, Fig. 1) and glomeruli (G, Fig. 1) were normal. There was atrophy of tubules and slight relative increase in interstitial connective tissue containing scattered

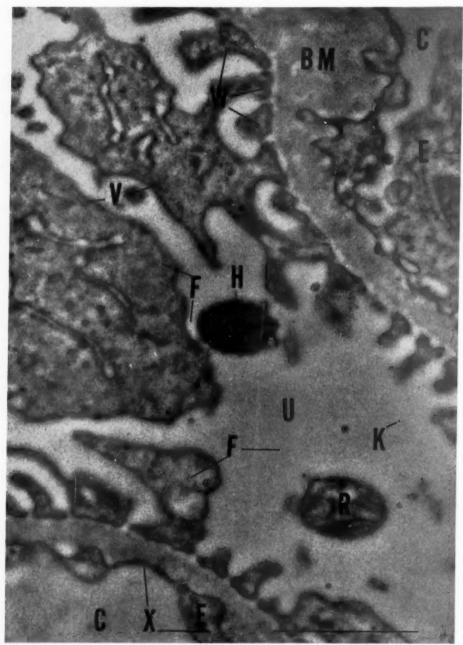


Fig. 5. Case II. Electronmicrograph of a portion of a glomerulus. Glomerular urine space (U) situated diagonally across the figure contains a hemosiderin granule (H), a free mitochondrion (R) and scattered ferritin (F). The pedicels (W) of the visceral epithelial cells (V) rest on glomerular basement membrane (BM). Portions of two capillary lumens (C) and their respective endothelial lining cells (E) may be seen at the upper right and lower left of the figure. At the lower left of the figure are several spots (X) which at this resolution have the same appearance as ferritin. None of these ferritin-like spots in the glomerular capillary lumen, endothelium or basement membrane, when viewed under higher resolution, demonstrated the characteristic sub-unit structure of ferritin. On close inspection some spots which might have been mistaken for ferritin proved to be defects in the film emulsion (K). Bar at lower right indicates 1 μ . Original magnification \times 40,500.

lymphocytes. Hemosiderin granules (H, Fig. 1) were seen, only rarely in the epithelial cells of glomeruli but in dense accumulations in the proximal tubule epithelial cell and occasionally in the epithelium of the distal tubule. Frequently the epithelial cells of the proximal convoluted tubules were obscured by

hemosiderin granules and the same material was found filling the lumen of tubules. No cellular reaction to the iron deposition was seen.

Case II. A forty-three year old white woman (C. F., C.G.H. No. 95350) was first seen at the

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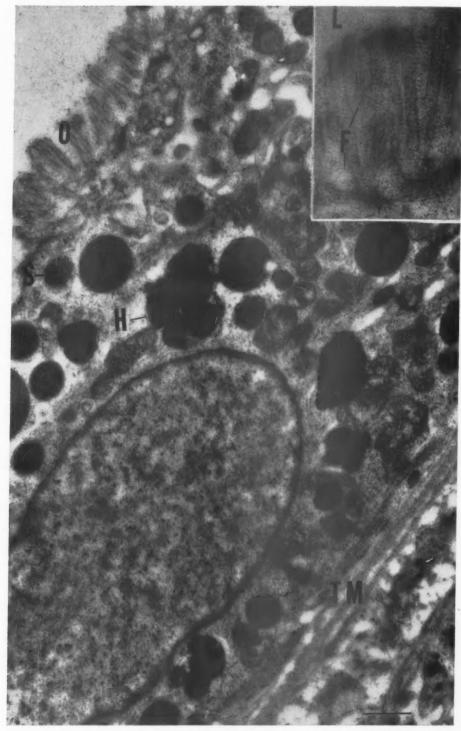


Fig. 6. Case II. Electronmicrograph of a portion of a proximal convoluted tubule cell containing hyaline droplets (Y), hemosiderin granules (H), siderosomes (S). A portion of the brush border (O) and tubular basement membrane (TM) may also be seen. Ferritin is difficult to distinguish at this relatively low magnification. Bar at lower right indicates 1 μ . Original magnification \times 13,500. *Inset*: Ferritin (F) is present in the brush border and in the lumen (L) especially in approximation to the brush border. Original magnification \times 40,500.

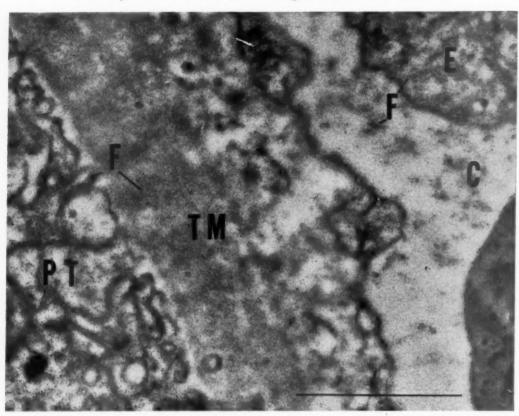


Fig. 7. Case II. Electronmicrograph of a portion of the base of a proximal convoluted tubule cell (PT), underlying tubular basement membrane (TM) and associated peritubular capillary endothelial cell (E) and lumen (C). Ferritin (F) may be seen in all areas, but most heavily concentrated within the tubule cell. Bar at lower right indicates 1 μ . Magnification \times 40,500.

Colorado General Hospital at age twenty-one in 1938. She was followed through two normal pregnancies at age twenty-one and twenty-two. The hemoglobin was normal (reticulocyte count not obtained). Urinalysis was normal but the urine was not tested for hemoglobin or hemosiderin.

She was next seen in February 1945 at age twentyeight at which time a diagnosis of paroxysmal nocturnal hemoglobinuria was made. In June 1944 she had been hospitalized elsewhere because of dark urine and proteinuria which had been attributed to nephritis. In the subsequent eight months she had noted several recurrences of dark urine and stated that "blood always appears in the morning and the urine clears as the day goes on." Laboratory data in 1945 revealed urine protein varying from 0 to 3 plus, hemosiderinuria 4 plus, whole blood hemoglobin 11.6 gm. per cent, plasma hemoglobin 105 mg. per cent, reticulocytes 0.6 to 1 per cent, serum bilirubin less than 2 mg. per cent, serum non-protein nitrogen 28 mg. per cent. The diagnosis of paroxysmal nocturnal hemoglobinuria was confirmed by a positive reaction to the Ham test [5].

The patient was next seen here in July 1958 when the following laboratory data were obtained: blood hemoglobin 9 gm. per cent; urine protein trace, the

sediment contained large amounts of hemosiderin; phenolsulfonphthalein excretion 35 per cent of 1 cc. of dye excreted in the urine twenty minutes after intravenous injection; blood urea nitrogen 11 mg. per cent; blood creatinine 1.3 mg. per cent. Kidney biopsy was performed on July 10, 1958.

During the eighteen months between July 1958 and December 1959 the patient was seen periodically in the clinic and continued to work full-time as a telephone operator. Her blood hemoglobin varied between 6.8 and 8.9 gm. per cent.

In December 1959 she was again hospitalized at the Colorado General Hospital and a second kidney biopsy was performed on December 1, 1959. At this time the following laboratory data were obtained: whole blood hemoglobin 6.3 to 8 gm. per cent, plasma hemoglobin 645 mg. per cent, reticulocytes 6.8 per cent, serum bilirubin conjugated 1.2 mg. per cent, free 6 mg. per cent, cholinesterase of plasma 0.98 delta pH units, of erythrocytes 0.27 delta pH units. The urea clearance was 89 per cent of normal, phenolsulfonphthalein excretion 35 per cent of 1 cc. of dye excreted twenty minutes after intravenous injection, blood urea nitrogen 13 mg. per cent. The result of the Ham test was positive [5].

On microscopic examination, the sections of both

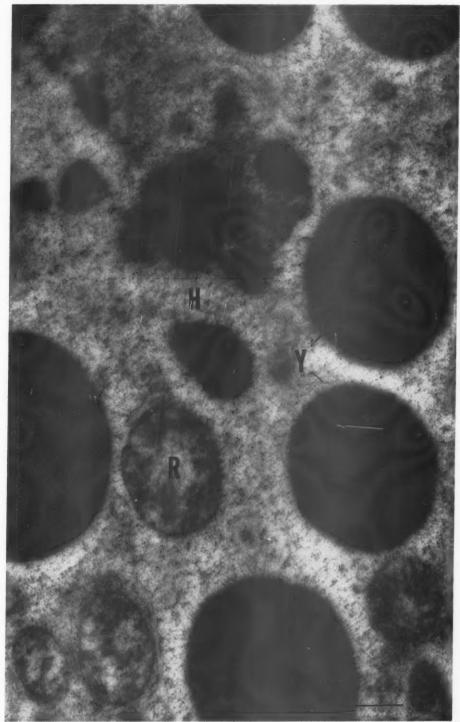


Fig. 8. Case 11. Electronmicrograph of a small area of a proximal convoluted tubule cell showing hemosiderin granules (H), mitochondria (R) and hyaline droplets (Y). The latter are relatively homogeneous electron-dense bodies containing peripheral foci of higher electron density (arrow). Bar at lower right indicates 1 μ . Original magnification \times 40,500.

biopsy specimens showed kidney tissue which included cortex and medulla and contained an average of 12 glomeruli per section. The arterioles (A, Fig. 2) and glomeruli (G, Fig. 2) were normal and the glomeruli only rarely contained 1 or 2 small hemo-

siderin granules in the cytoplasm of the epithelial cells. The cytoplasm of epithelial cells of the proximal convoluted tubules (PT, Fig. 2) contained many coarse hemosiderin granules. (H, Fig. 2.) In some tubules the hemosiderin granules obliterated both

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cytoplasmic and nuclear detail. Less frequently the lumen of a tubule was filled with a cast (J, Fig. 3) containing hemosiderin granules. There were few hemosiderin granules in the epithelial cells of the distal convoluted tubules. (DT, Fig. 3.) No inflammatory or connective tissue reaction to the hemosiderin deposition was seen. The interstitial tissue was normal.

Upon examination with the electron microscope, electron dense particles of uniform density and size (50 to 60 Å) were found at various sites in the nephron. These particles, when seen at high magnification (× 240,000), consisted of 15 to 20 Å sub-units 15 to 20 Å apart (arrow, Fig. 4) indistinguishable in mor-

phology from the ferritin molecule [4].

Ferritin was found as individual particles (F, Fig. 5, 6 inset, and 7), as membrane-limited masses (siderosomes) (S, Fig. 6), and as larger non-membranelimited clumps (hemosiderin granules). (H, Fig. 5, Fig. 6, and Fig. 8.) Ferritin appeared in moderate concentration in the glomeruli, within visceral epithelial cells (V, Fig. 5), in the urine space (U, Fig. 5) and in the parietal epithelial cells of Bowman's capsule. Ferritin was found in high concentration in the proximal tubule within the tubule lumen (L, Fig. 6 inset), within the epithelial cell membrane at the brush border (Fig. 6 inset) and within the epithelial cell cytoplasm. (Fig. 7 and 8.) There were also moderate concentrations of ferritin within the distal tubule epithelial cells, the basement membrane underlying the distal and proximal tubule epithelial cells (TM, Fig. 7), and in the adjacent peritubular capillary lumen (C, Fig. 7) and endothelium. (E, Fig. 7.) Mitochondria contained ferritin in low concentration. (R, Fig. 8.)

Ferritin was not seen in the glomerular capillary lumens, the glomerular capillary endothelium or the glomerular capillary basement membrane. The lower magnification electron micrographs (× 40,500) (Fig. 5) did show an occasional particle of approximately the same size as ferritin. Some of these were defects in the film emulsion (K, Fig. 5), others were of uncertain identity. (X, Fig. 5.) None of the latter particles when viewed under high magnification (× 240,000) showed the sub-unit structure (Fig. 4) characteristic of

ferritin.

Relatively large numbers of hyaline droplets (Y, Fig. 6 and Fig. 8) were observed in tubular epithelial cells. They were relatively homogeneous electron dense bodies within which were circumferentially located high electron density masses. (Arrow, Fig. 8.)

COMMENTS

Several characteristics of paroxysmal nocturnal hemoglobinuria which relate to its pathologic physiology have been described. The diagnostic abnormality of this disease is an increased sensitivity of the erythrocyte to hemolysis in an acid medium [6]. Lysis requires the

presence of complement, properdin and magnesium [7]. A marked deficiency of erythrocyte acetylcholine esterase activity has been described [8]. The presence of an associated structural abnormality of the erythrocyte has been debated by electron microscopists [9,10]. Paroxysmal nocturnal hemoglobinuria is the most common disease in this country with chronic intravascular hemolysis and chronic hemoglobinemia, hemoglobinuria and hemosiderinuria.

The factors which govern filtration of hemoglobin at the glomerulus in hemoglobinemia have been studied recently [11,12]. Hemoglobinuria has been shown to occur only after saturation of haptoglobin, the hemoglobin-binding protein present in normal serum [11]. Hemoglobin in excess is then free in the serum and available for glomerular filtration [12]. Although serum haptoglobin was not measured in our patients, it has been shown to be present in lower than normal concentrations in patients with various types of hemolytic anemia [13].

The fate of hemoglobin in the nephron unit once it has been filtered at the glomerulus is similar to that of other proteins. Studies of the structural changes in the nephron following glomerular filtration of various proteins have indicated that filtered protein is reabsorbed in the proximal convoluted tubule where hyaline droplets appear [14]. That reabsorption of filtered hemoglobin takes place in the proximal nephron has been demonstrated in animals by stop-flow technics [15]. Tubular reabsorption of hemoglobin in animals has been shown to result in the deposition of iron in the renal tubule as ferritin [16] and hemosiderin [17].

Intense renal hemosiderosis is the most characteristic feature of the pathology of paroxysmal nocturnal hemoglobinuria. This finding is not pathognomonic for paroxysmal nocturnal hemoglobinuria and has also been described in other conditions in which there is intravascular hemolysis and in hemochromatosis [78].

The pathologic findings in paroxysmal nocturnal hemoglobinuria were reviewed by Heitzman [19] in 1953. In eighteen previously reported autopsy cases and in the case described by him, the most characteristic abnormality was a striking deposition of iron in the renal tubules. Heitzman's case in which the patient was autopsied after seven years' known duration of disease showed considerable renal interstitial fibrosis which the authors considered to have resulted from the deposition of iron. Of the two

patients described herein, one (Case 1), autopsied after at least eighteen years' duration of disease, showed only slight interstitial fibrosis of the kidney despite intense deposition of iron and the other (Case II), in whom biopsy was performed after at least sixteen years' duration of disease, showed no interstitial fibrosis of the kidney despite intense deposition of iron. Renal function in both patients evaluated clinically, was normal. The absence of structural or functional reaction to iron in the two patients described in this paper suggests that the interstitial reaction described in other patients may have been coincidental and not related to the deposition of iron.

The patient with paroxysmal nocturnal hemoglobinuria provides a clinical counterpart to the animal experiments in which the fate of hemoglobin filtered at the glomerulus has been studied [16,17]. Examination of renal tissue from our patient (Case II) with the electron microscope revealed the precise location of the transformation of hemoglobin into ferritin in the

nephron.

The catabolism of hemoglobin in the kidney yields iron-containing particles visible under the electron microscope as iron micelles [3]. The 50 to 60 Å size particles herein described, when resolved to 15 Å, are seen to consist of individual 15 to 20 Å size particles and are thus indistinguishable from the iron micelles of the ferritin molecule [4]. It has been demonstrated in experimental hemosiderosis produced by intraperitoneal injection of hemoglobin that ferritin is one of the constituents of hemosiderin [3].

At sites where ferritin is demonstrated, its rate of accumulation must exceed its rate of disposition. Ferritin was not demonstrated in the glomerular capillary lumen, endothelium or basement membrane; if it is present there, it must be in very low concentration. Ferritin was seen in the visceral glomerular epithelium, glomerular urine space, parietal glomerular epithelium, tubule lumen and in greatest concentration in the tubule epithelial cell. Ferritin was also seen in the tubule basement membrane, peritubular capillary lumen and endothelium. This pattern of concentration gradient indicates that ferritin may be formed from filtered hemoglobin in epithelial cells of the nephron, to a lesser degree in those of the glomerulus and maximally in those of the convoluted tubule.

The key point indicating that the major source of ferritin in the tubular epithelial cell is

hemoglobin filtered at the glomerulus rather than ferritin transported from the peritubular capillaries is the presence of ferritin in very low concentration (if at all) in the glomerular capillary lumens, endothelial cell and basement membrane. The possibility that ferritin in the tubule epithelial cell is formed from hemoglobin transported into the cell from the peritubular capillaries is rendered unlikely by experimental work indicating that the renal tubule epithelium does not secrete hemoglobin but reabsorbs it from the tubule lumen [15]. However, the transport of a small amount of ferritin into the epithelial cell from the peritubular capillaries cannot be ruled out.

On the other hand, the presence of a much higher concentration of ferritin in the peritubular capillaries than in the glomerular capillaries suggests that ferritin may move from the cytoplasm of the proximal tubule epithelial cell across the peritubular basement membrane, and through the peritubular capillary endothelium into the lumen of the peritubular capillaries and from these into the general venous circulation. Whether this observation may be interpreted to indicate that the entire large ferritin molecule (molecular weight 600,000) is transported intact into the lumen of the peritubular capillaries remains uncertain. Richter [22] has presented evidence indicating that in mice given iron parenterally, the intracellular quadruplets of 20 Å iron hydroxide micelles are enveloped by apoferritin. Several workers have demonstrated that ferritin visible as iron hydroxide micelles is capable of considerable mobility: in man, from reticulum cells to erythroblasts [23,24]; in rats given ferritin intravenously, from the intravascular compartment into rat muscle capillary endothelium [25], and from the intravascular compartment into the glomerular urine space by passage through glomerular endothelium, basement membrane and epithelium [26]. To this list, may now be added: in man (with paroxysmal nocturnal hemoglobinuria), from the renal tubule epithelium across the peritubular capillary basement membrane and endothelium into the peritubular capillaries.

The amount of iron returned to the general circulation as ferritin is probably small and the main route by which iron leaves the kidney is in the urine as hemoglobin, ferritin and hemosiderin. Transport of ferritin from the renal tubule epithelial cell to the peritubular capillaries and systemic venous circulation is insignifi-

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cant in the iron economy of the patient with paroxysmal nocturnal hemoglobinuria. However, this transport, although it may be small in amount, is of biologic significance and indicates that the current concept of ferritin metabolism which limits its function to intracellular storage of iron [27] may require modification.

The accumulation of ferritin in the epithelial cells of the glomerulus and Bowman's capsule demonstrates a functional similarity with respect to hemoglobin catabolism between these cells and tubule epithelium. Although structurally different, these epithelial cells are closely related

embryologically [20].

The proximal tubule epithelial cell was the site of maximal accumulation of ferritin. It was found in the cytoplasm in small aggregates in association with electron dense material and in large non-membrane-limited aggregates which probably constitute the hemosiderin granules visible on light microscopy. It also occurred sparsely in hyaline droplets, which were different in structure from those previously described [21], and mitochondria; and densely in siderosomes indistinguishable from those demonstrated in animals after intraperitoneal injection of hemoglobin [3].

Several problems remain matters of speculation. What is the source of siderosomes? Are they derived from mitochondria, hyaline droplets or neither? Does ferritin first appear as single units, small aggregates, large aggregates, within siderosomes, within mitochondria or within hyaline droplets? What are the interrelations of ferritin in these various locations and the path over which it travels through the cell? The structural changes observed here do not permit any answers to these questions.

The localization of iron in the nephron in paroxysmal nocturnal hemoglobinuria is then consistent with the following hypothesis. Filtered hemoglobin is reabsorbed by epithelial cells, particularly in the proximal tubule. Within these cells hemoglobin is catabolized and hemosiderin and ferritin appear. The possibility that hemoglobin or ferritin enter tubule cells from peritubular capillaries is less likely but has not been ruled out. Iron as ferritin appears mainly in the proximal tubule epithelial cell cytoplasm and therefore its rate of accumulation here must greatly exceed its rate of disposal. The iron accumulated as ferritin may leave the epithelial cells of the nephron by several routes: (1) ferritin may be secreted by the epithelial cell into

the lumen; (2) the tubule cell may be sloughed into the tubule lumen and its contents including ferritin and hemosiderin leave the body via the urine; (3) ferritin may pass through the peritubular basement membrane and enter the general circulation via the peritubular capillaries; (4) the iron may be changed to a nonferritin form and leave the nephron cell by routes 1, 2 or 3. Histologic evidence that both 2 and 3 occur has been presented.

This pathway of hemoglobin and ferritin movement is consistent with light microscopic observations of protein reabsorption in the proximal tubule [13]; the demonstration of hemoglobin reabsorption in the proximal nephron [15]; electron microscopic observations of the structural changes in the kidney which follow intraperitoneal injection of hemoglobin in rats [19]; and Marchiafava's designation of this as a disease in which there is perpetual hemosiderinuria.

SUMMARY

The pathologic changes seen on light and electron microscopy of the kidney in paroxysmal nocturnal hemoglobinuria are described in two cases, one at autopsy and the other at biopsy.

Intense hemosiderosis of the kidney is the most characteristic pathologic change in paroxysmal nocturnal hemoglobinuria although not specific for this disease. There is no apparent structural or functional reaction to the hemosiderosis.

The intensity of ferritin accumulation at various points in the nephron is correlated with current concepts of hemoglobinuria, hemoglobin and ferritin metabolism and large molecule transport.

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Immunologic Factors and Resistance to Infection in Chronic Lymphatic Leukemia*

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Patients with chronic lymphatic leukemia may be particularly susceptible to infection [1–3], and in many instances death is due to infectious rather than hematologic complications. The disturbances leading to infections in neoplastic diseases of the lymphoid and reticuloendothelial system appears to differ from those in disseminated carcinomatosis. As Kushner and Thomas [4] have pointed out, infection in carcinoma is most frequently related to local problems of tissue derangement such as ulceration, obstruction or perforation. While these local factors may operate from time to time in the lymphomas, they contribute little to an understanding of the general problem of infection in these diseases.

The increased susceptibility to infections occurring in patients with chronic lymphatic leukemia requires definition beyond the generality of "decreased host resistance." Gross, Gitlin and Janeway [5] are of the opinion that the occurrence of infection can be attributed to a deficiency of granulocytes. Jim [6], Hudson and Wilson [7] and others [8-10] have reported hypogammaglobulinemia in the course of chronic lymphatic leukemia. Other factors, subject to investigation, are the ability of the patient to produce circulating antibodies, bacterial-type allergy or delayed hypersensitivity, complement and properdin levels, and the direct or indirect effects of the drugs used in the therapy of the disease.

It is the purpose of this paper to correlate some of these factors with host resistance to infection in chronic lymphatic leukemia and to compare the clinical status of patients with and without infectious complications.

MATERIALS AND METHODS

Twenty-two patients with chronic lymphatic leukemia were studied. In all, marrow and peripheral blood findings were compatible with this diagnosis. These patients were selected according to their infectious disease history and divided into two groups, group A for patients with chronic lymphatic leukemia who had a history of chronic or recurrent infectious disease problems and group B for patients who had no such history. A third group of twenty patients (group C) with neoplasms other than chronic lymphatic leukemia, some with infectious problems as well, was used as an additional control group for some of the tests.

The patients in groups A and B were compared as to age, sex, duration of disease, clinical and hematologic findings at the time of study. A detailed study of the entire clinical course and the pathologic features of the patients in group A is reported separately [11].

A spectrum of studies was completed in most of the patients.

Hematologic examination was performed by conventional methods; granulocytes were enumerated by differential leukocyte counting of Wright-Giemsa stained smears of peripheral blood. Serum proteins were studied by electrophoresis; the titer of macroglobulins was determined immunologically. Circulating antibodies were estimated by isohemagglutinin titers and response to typhoid-paratyphoid A and B (TAB) vaccination. The titer of the former would be an estimation of the ability to maintain production of antibodies which existed prior to the development of leukemia while, in most cases, TAB vaccination would determine ability to respond to a new antigenic stimulus. Delayed hypersensitivity or bacterial-type allergy was evaluated by skin testing with tuberculin, mumps and Candida albicans antigens. In addition, complement and properdin titers were also determined.

Serum electrophoresis: For each specimen the deter-

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Patient	Age, (yr.) and Sex	Duration of Disease (mo.)*	Hemo- globin (gm. %)	Platelets (1,000/ cu. mm.)	White Cell Count (1,000/ cu. mm.)	Mature Granu- locytes (%)†	Mature Granu- locytes (ab- solute no.)	Liver Size‡	Spleen Size‡	Lymph Nodes§	Therapy and Status of Diseases
		1			Group A (Fi	requent Infe	ctions)				
M. S. J. D. H. S. J. Po. R. P. L. B. P. M. S. W. A. R. C. K. M. K.	77,M 49,M 55,M 68,M 53,F 72,M 43,F 48,M 39,M 67,M 57,F	126 111 89 22 0 60 60 48 0 34 131 Mean 64.6	11.7 12.0 13.0 10.0 13.5 12.8 9.0 11.4 7.5 10.6 10.8	107.8 292.8 53.3 293.7 50.9 136.5 13.6 77.2 82.7	72.0 24.1 13.0 115.0 27.9 12.1 471.0 77.0 420.0 112.0 65.0	23 11 29 10 39 1 1 1 2 2	16,560 2,651 3,770 11,500 10,981 4,710 770 4,200 2,240 1,300	1 5 0 7 0 1 6 5 4 12 6	0 9 10 13 1 0 9 4 7 14 6	G, 3+ G, 2+ 0 G, 3+ R, 2+ R, 4+ 0 G, 4+ G, 3+ G, 3+ G, 1+	None (+) Prednisone (+) Prednisone (+) None (0) Chlorambucil (+) X-ray (+) Prednisone (+) Prednisone (-) Prednisone (-) Phosphonitrile (+) X-ray (-)
			1	(Group B (Inf	requent Info	ections)				
N. S. A. H. J. Pe. C. S. E. G. V. B. H. O. H. Ha. S. L. S. L. H. He. G. M.	44,M 51,F 57,F 62,M 66,F 70,F 63,M 41,M 74,F 58,M 50,F	42 50 27 58 152 96 14 36 60 38 168 Mean 68.2	15.1 13.5 11.6 12.4 13.1 12.4 9.0 10.9 9.9 10.2 11.5	221.2 229.3 224.0 161.0 302.1 39.9 108.0 21.6 67.9 67.2	110.0 52.0 101.0 170.0 11.2 4.4 172.0 90.0 116.0 78.0 107.0	5 7 5 11 13 1 5 3 7 20	5,500 3,640 5,050 16,700 572 1,720 4,500 3,480 546 21,400	2 2 1 5 1 4 5 9 6 0 6	3 1 0 7 0 14 0 20 0 23 0	G, 2+ G, 2+ R, 1+ 0 0 0 G, 2+ R, 2+ G, 2+ G, 2+	None (+) None (+) None (+) None (+) None (+) None (+) None (0) None (0) Chlorambucil (+) Prednisone (+) 6-Methyl prednisolone (-)

* For patients in group A, this is the period from diagnosis to onset of infectious complications. For patients in group B, this is the period from diagnosis to first serum electrophoretic study.

† Polymorphonuclear and band form neutrophilic leukocytes.

Centimeters below costal margin.

§ R = regional; G = generalized lymphadenopathy; 1+ = nodes up to 1 cm.; 2+ = nodes up to 2 cm., etc.

|| Antileukemic therapy at the time of this study; (+) = disease satisfactory or improving as a result of therapy; (0) = disease progressing and in need of therapy; (-) = disease progressing, little or no response to therapy.

mination was performed in duplicate on an eight-strip Spinco Model R paper electrophoresis cell using 3 cm. paper strips (Whatman No. 308-028). The stained strips were analyzed with a calibrated recording photometer and automatic integrator and expressed in grams per cent of protein.

Macroglobulins: The level of these proteins was estimated immunologically by the Ouchterloney geldiffusion technic utilizing the procedure described by Korngold and Van Leeuwen [12]. Serum with a negative reaction at 1:10 dilution was considered deficient.

Isohemagglutinins: The serum to be tested for isohemagglutinins was diluted with saline solution by standard serial dilution methods. Washed red cells were suspended in saline to make a 2 to 3 per cent preparation. An equal volume of suspension of cells of the appropriate type was added to each tube and allowed to incubate at room temperature for one hour. The mixture was then centrifuged, agitated and examined grossly for agglutination. The tube following the last tube to show gross agglutination was examined

microscopically and this procedure was continued until no agglutination was seen.

Response to typhoid-paratyphoid A and B vaccination: The typhoid and paratyphoid vaccine employed contained, per cubic centimeter, 1,000,000,000 killed typhoid bacilli, 250,000,000 killed paratyphoid A and 250,-000,000 killed paratyphoid B bacilli. Each patient received three subcutaneous injections of 0.5 cc. of vaccine at least one week apart. If more than one month elapsed between injections the entire series was repeated. Blood was taken for antibody response three to four weeks after the last vaccination. Serum specimens to be tested for agglutinating antibodies were set up with four antigens using a microscopic slide method. The antigens were B. typhosus O, B. typhosus H, B. paratyphosus A and B. paratyphosus B. Antigens used for the diagnostic slide agglutination were prepared according to the method of Welch and Stuart [13]. Only agglutination in dilutions of 1:20 or greater was considered significant. The results of the agglutination tests prior to vaccination were negative in each case.

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TABLE II VALUES OBTAINED BY PAPER ELECTROPHORESIS OF THE SERUM OF PATIENTS IN GROUPS A, B AND C

D	Total Protein	Albumin		Globuli	ns (gm. %)	
Patient	(gm. %)	(gm. %)	Alpha ₁	Alpha ₂	Beta	Gamma
	G	roup A. Chronic	Lymphatic Leukemi	a (Frequent Infection	ons)	
M. K.	7.1	3.39	0.48	1.60	1.15	0.48
C. K.	5.4	3.43	0.31	0.50	0.59	0.58
M. S.	7.5	4.65	0.29	0.88	1.00	0.68
A. R.	6.7	3.83	0.45	0.91	0.83	0.63
J. D.	6.3	4.20	0.31	0.60	0.88	0.31
L. B.	6.3	3.60	0.39	1.08	0.89	0.34
H. S.		3.06	0.45	0.90	0.90	0.18
R. P.	6.1	2.93	0.41	1.08	1.19	0.49
P. M.	4.9	2.76	0.42	0.73	0.78	0.21
J. Po.	6.7	4.05	0.26	0.68	1.36	0.35
S. W.	6.3	3.53	0.46	0.90	1.12	0.31
	Gr	oup B. Chronic L	ymphatic Leukemia	(Infrequent Infecti	ions)	
C. S.	7.2	3.90	0.40	1.08	0.91	0.91
S. L.	5.9	2.93	0.26	1.02	1.07	0.62
E. G.	7.6	3.89	0.30	1.03	1.37	1.01
H. O.	6.9	3.43	0.33	0.92	1.11	1.11
J. Pe.	6.9	4.40	0.21	0.50	0.96	0.84
Н. На.	6.1	3.00	0.31	0.35	0.57	1.87
G. M.	5.4	2.83	0.30	0.69	0.98	0.67
H. He.	6.5	3.27	0.35	0.96	1.12	0.80
A. H.	7.5	4.05	0.34	0.60	0.96	1.56
N. S.	8.4	4.60	0.37	0.50	1.35	1.57
V. B.	9.4	4.61	0.39	0.92	1.19	2.30
		Gr	oup C. Other Neop	lasms		
M. P.*	8.0	3.83	0.48	1.03	1.17	1.51
P. E. *	7.7	3.84	0.44	0.80	1.03	1.59
M. R.*	8.3	3.39	0.45	0.80	1.13	2.55
P. B. *	7.1	3.03	0.36	0.81	1.50	1.41
R. B. *	7.2	2.64	0.33	0.84	1.55	1.86
B. D. *	6.2	2.44	0.43	0.85	0.94	1.56
F. J.†	7.1	3.50	0.31	1.04	0.93	1.33
H. B.†	6.3	3.15	0.37	0.85	0.89	1.05
B. W.†	5.9	1.79	0.31	0.89	1.43	1.48
I. G.†	7.2	3.64	0.23	0.72	1.39	1.21
F. D. ‡	6.5	2.59	0.29	0.88	1.34	1.40
M. N. 1	7.4	3.74	0.47	0.84	1.08	1.28
J. P.‡	6.6	2.32	0.50	1.13	1.29	1.36
J. N. §	6.8	2.66	0.32	0.91	1.20	1.71
L. R.	7.5	1.71	0.46	1.17	1.63	2.53
F. T. ¶	5.4	2.47	0.47	0.77	0.90	0.80
Z. L. **	6.9	2.55	0.45	1.16	1.32	1.43
C. F. ††	6.2	2.55	0.62	0.89	1.18	0.97
D. S. ‡‡	6.7	2.72	0.47	0.96	1.05	1.51
P. C. §§	5.0	1.90	0.40	0.93	0.77	1.00
rmal values	6.5-7.9	3.75-5.23	0.13-0.29	0.31-0.89	0.48-1.06	0.63-1.77

^{*} Carcinoma of the breast.

[†] Carcinoma of the prostate.

Chronic myelogenous leukemia.

Carcinoma of the lung.

Carcinoma of the cervix.

[¶] Carcinoma of the bladder.
** Carcinoma of the larynx.

^{††} Neuroblastoma.

^{‡‡} Mycosis fungoides.

^{§§} Hodgkin's disease.

TABLE III SUMMARY OF SERUM PROTEIN FINDINGS

	Group A			Group B			Group C		
Serum Protein	Decrease	Nor- mal	Increase	Decrease	Nor- mal	Increase	Decrease	Nor- mal	Increase
Albumin	7	4		5	6		18	2	
α_1 globulin		2	9		2	9		2	18
α2 globulin		5	6		5	6		12	8
β globulin		7	4		5	6		7	13
γ globulin	9	2		1*	8	2		17	3
Macroglobulins	7	2		1	9				

^{*} Borderline value.

Tuberculin, mumps and C. albicans skin tests: Tuberculin purified protein derivative was employed in a dose of 2×10^{-7} gm. per each 0.1 cc. injection (intermediate strength). Freshly prepared mixtures were used for all tests. The skin test antigen for mumps virus hypersensitivity was prepared with ultraviolet light inactivated virus grown in embryonated chicken eggs. Each 1 cc. of skin test antigen contained twenty complement-fixing units. C. albicans skin tests were performed with a 1:1,000 dilution of mold extract.* In each case, 0.1 cc. of the skin test antigen solution was injected intradermally into the volar surface of the forearm with at least 5 cm. between injection sites. All test results were read in forty-eight hours. A positive reaction was recorded for the tuberculin and C. albicans skin tests when the injection site showed a palpable area of induration at least 6 mm. in diameter with or without redness. A positive reaction to the mumps skin test required an area of erythema at least 1.5 cm. in diameter, with or without induration.

Complement and properdin titers: Total complement and components were assayed by the technic of Ecker et al. [14] except that a 50 per cent hemolysis end point was used instead of 100 per cent. The hydrazine method was used for preparation of serum without the fourth component of complement. The per cent of hemolysis was estimated by visual comparison with standards prepared from the same erythrocyte suspension used for the tests. Properdin was determined by zymosan (hemolytic) assay as described by Pillemer et al. [15].

RESULTS

Comparison of the Clinical and Hematologic Findings in Patients in Groups A (Frequent Infections) and B (Infrequent Infections). In Table 1 the patients in groups A and B are listed by age, sex, duration and extent of disease, and requirement for

Provided by the courtesy of the Hollister-Stier Laboratories, Philadelphia, Pennsylvania.

and response to treatment. There were no consistent differences between the two groups in regard to leukocyte counts or absolute number of mature granulocytes, hepatosplenomegaly and lymphadenopathy.

There was some difference in the tempo of progression of the disease, as indicated by requirement for treatment and clinical status. In group A only two patients did not require treatment at the time of the study, and the entire group had required and received treatment prior to the study. All eleven of these patients have died since this study was completed. In group B eight of the eleven patients did not require treatment at the time of this study. Two patients not requiring treatment had never been treated for their leukemia; of the three others in this group one had been treated for symptomatic nodes only, and two patients had splenic radiation twelve and three years prior to this study. Two of the eleven patients have since died.

In group A, the average duration of disease from the time of diagnosis to the onset of chronic infectious complications was 64.6 months, as compared to 68.2 months from the time of diagnosis to the beginning of this study (first serum electrophoresis) for group B.

Study of Serum Proteins (Serum Electrophoresis and Titer of Macroglobulins). The initial paper serum electrophoresis determinations at Memorial Center for the three groups are presented in Table II. The alterations for each group may be summarized, together with the macroglobulin levels, as shown in Table III.

A scattergram of the gamma globulin values in three groups is given in Figure 1.

The patients with neoplastic disease studied

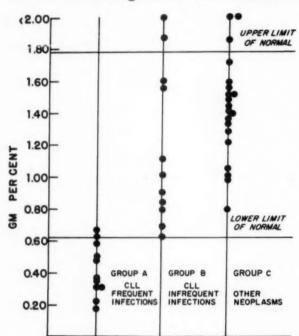


Fig. 1. Serum electrophoretic determination of gamma globulin in three groups of patients. Group A, chronic lymphatic leukemia (frequent infections). Group B, chronic lymphatic leukemia (infrequent infections). Group C, other neoplasms.

herein characteristically present a tendency toward decrease in albumin and elevation in alpha₁, alpha₂ and beta globulins. The gamma globulin levels were usually normal or elevated in groups B and C, and lowest in group A (chronic lymphatic leukemia with infectious complications). Decreased macroglobulin levels were associated with low gamma globulin levels.

Circulating Antibodies: Titer of Isohemagglutinins and Response to TAB Vaccination. Titer of isohemagglutinins: The titers obtained were not the result of antibody stimulation with blood group substances, and therefore may not represent the maximal level of these antibodies. The absence or marked decrease in isohemagglutinins was striking in patients with chronic lymphatic leukemia, the titer being less than a 1:16 in four of nineteen patients, and not detectable in six. However, in group B titers were 1:128 or higher in three patients. In contrast, the titers in six patients studied in group C were 1:16 or higher. There was no significant difference in the distribution of low isohemagglutinin levels in groups A and B, and low levels thus did not correlate with the level of gamma globulin or the infectious history.

Typhoid-paratyphoid A and B vaccination: None of the patients in group A (eight tested) responded to TAB vaccination. Four of eleven patients in group B had measurable antibody titers. These four also had normal gamma globulin levels and produced isohemagglutinins. Six of the seven vaccinated patients in group C produced antibodies.

Delayed Hypersensitivity Reactions: Tuberculin, Mumps and C. Albicans. Seven patients were studied in group A and eleven in group B.

Tuberculin: Two patients in group A had positive reactions; both had hypogammaglobulinemia and died of infection. Seven patients in group B had positive reactions; one of these patients had a low normal level of gamma globulin, the other six had normal levels.

Mumps: In group A two patients gave positive results. One patient (J. Po.) gave a positive reaction to all three skin tests. The second patient had a positive reaction to this antigen only. In group B nine patients tested gave positive reactions. Of the two remaining patients, one did and the second did not react to tuberculin and C. albicans antigen. Three patients, who had negative reactions to tuberculin and C. albicans antigen, reacted to mumps antigen.

Candida albicans: Two patients in group A had positive reactions. These were the same patients who had positive tuberculin reactions. In group B, six patients had positive reactions. All six had positive tuberculin reactions. There was one patient with a positive tuberculin reaction who gave a negative reaction to C. albicans.

With the exception of one patient, there was complete correlation between positive and negative responses to tuberculin and C. albicans antigen. The test for responsiveness to mumps vaccine was the only determination of viral immune response performed. Clinically, none of these patients had active tuberculosis, troublesome monilia infections or clinically apparent viral infections.

Complement and Properdin. In group A, complement levels were determined in seven patients and properdin levels in nine; all eleven patients in group B and six patients in group C were so studied. Total complement, its four components, separately, and properdin levels were assayed. There was no correlation between the diagnoses and infectious histories in groups A, B and C and the complement and properdin levels.

COMMENTS

The purpose of these studies was to determine if there were consistent hematologic or im-

Table IV
CORRELATION OF INFECTIOUS COMPLICATIONS WITH IMMUNOLOGIC STUDIES

				Typhoid-	S	kin Tests				
Patient	Infections	Gamma Globulin	Isohem- agglutinins	Paratyphoid A and B Antibodies	Tuberculin	Mumps	C. Albi- cans*	Comple- ment*	Pro- perdin	Therapy
N. S.	None	N	+	+	+	+	+	N	N	None
A. H.	None	N	+	+	+	+	+	N	N	None
J. Pe.	None	N	+ 1	+	+	+	+	N	N	None
C. S.	None	N	+	+	0	+	0	N	N	None
E. G.	None	N	+	0	+	+	0	N	N	None
V. B.	Infrequent	High	+	0	+	0	+	N .	N	None
H. He.	Infrequent	N	+	0	+	+	+	N	N	Prednisone
H.O.	Infrequent	N	0	0	+	+	+	N	Ab.	None
Н. На.	Infrequent	High	0	0	0	+	0	N	N	None
S. L.	Infrequent	BL	+	0	0	0	0	N	Ab.	Chlorambucil
G. M.	Infrequent	BL	0	0	0	+	0	Ab.	N	6-Methyl prednisolon
M. S.	Recurrent	BL	+	0	0	0	0	N	Ab.	None
J. D.	Recurrent	Low	+	0	0	+	0	N	Ab.	Prednisone
H. S.	Recurrent	Low	0	0	0	0	0	N	N	Prednisone
J. Po.	Recurrent	Low	+	0	+	+	+	N	N	None
R. P.	Recurrent	Low	+	0	0	0	0	N	N	Chlorambucil
L. B.	Recurrent	Low	0	0	+	0	+		N	X-ray
P. M.	Recurrent	Low		0	0	0	0	N	Ab.	Prednisone
S. W.	Recurrent	Low	0	0				Ab.	N	Prednisone
A. R.	Recurrent	BL				***		+ < +		Prednisone
C. K.	Recurrent	Low	+						Ab.	Phosphonitrile
M. K.	Recurrent	Low								X-ray

Note: N = normal; Ab. = abnormal (diminished); BL = borderline; + = present; 0 = absent. *Includes total and all fractions.

munologic changes which could be correlated with the occurrence of chronic infections in some patients with chronic lymphatic leukemia. The most consistent finding was a decrease in serum gamma globulin level, as determined by serum electrophoresis. Chronic and recurrent infections were associated with values of 0.70 gm. per cent or less. This observation is consistent with other reports [8,10]. However, in children with congenital hypogammaglobulinemia, it is generally considered that levels of 0.10 to 0.15 gm. per cent are sufficient to protect them from most infections [16]; in patients with chronic lymphatic leukemia apparently even a mild decrease in gamma globulin levels may be attended by infectious complications. Janeway and Gitlin [16] have made the further observation that in patients with acquired agammaglobulinemia the level of gamma globulin associated with infection is higher than in those with the congenital form. The functional activity of the gamma globulin doubtless makes the important difference, but none of the tests performed in this study allow us to determine what functional quality of gamma globulin was lost along with the diminished quantity.

Low isohemagglutinin titers were found in

patients with chronic lymphatic leukemia, but they were not associated necessarily with infection. Similarly, the skin tests and the complement and properdin levels did not differ significantly between groups A and B. There was a definite difference in the response of the patients with chronic lymphatic leukemia to typhoid-paratyphoid antigen stimulation; those with chronic lymphatic leukemia and frequent infection showed no antibody response, whereas four of eleven patients in group B without infection produced antibodies. Failure to respond to the antigens, however, was not in itself a sign of increased susceptibility to infection.

The relation of the infectious process to the various immunologic studies is summarized in Table IV. The most important correlation with infection is the low gamma globulin level. Despite failure of any determination to evaluate the functional activity of gamma globulin, it is apparent that the lower the gamma globulin level the poorer the antibody response.

If the patient has a decreased quantity of gamma globulin, it may be expected that infectious processes will complicate the course; there were no exceptions to this generalization in this group of twenty-two patients, or in fourteen

additional patients with chronic lymphatic leukemia subsequently studied. It appears that in other diseases, gamma globulin levels may be abnormally low without a predilection for infection. Recently a patient with hypogammaglobulinemia and pernicious anemia was seen at this institution. A gamma globulin level of 0.27 gm. per cent was not associated with infectious complications [17]. In this patient one would presume that the decrease in gamma globulin was not associated with a significant loss of antibody function or that it was non-antibody

gamma globulin that was lost. Low gamma globulin levels may not signify diminished or absent antibody production. An anomalous situation occurs when a patient with hypogammaglobulinemia and poor antibody response manifests clinical allergies. Two of our patients (H. S. and S. W.) were allergic to penicillin; one (H. S.) was allergic to morphine as well. Two patients (J. D. and H. S.) had mild anaphylactoid reactions after an injection of gamma globulin; one (P. M.) had severe febrile reactions to blood transfusions (negative reaction to Coombs' test). The isohemagglutinins and reagins of atopic hypersensitivity are beta globulins. Hemolytic anemia has been described in patients with agammaglobulinemia [18,19]. There is an unusually high incidence of arthritis resembling the rheumatoid type in children with agammaglobulinemia [16]. Witness to the subtlety of these poorly understood changes is our patient (H. S.) who was severely hypogammaglobulinemic with recurrent pneumococcal infections, allergic to penicillin, morphine and gamma globulin, but whose hay fever never returned once chronic lymphatic leukemia had developed. In patients with normal or high gamma globulin levels and chronic lymphatic leukemia infections may develop and they may show poor resistance, but chronicity and recurrences have not been as characteristic in this group as in the hypogammaglobulinemic patients. It is well recognized that normal and even elevated levels of gamma globulin may be associated with poor antibody function [20,21]. In chronic lymphatic leukemia one may also consider the leukemic cells to arise from a clone with a specialized antibody function which would then be exaggerated with proliferation of this cell type.

It would be of great interest to determine just what function of gamma globulin is lost in these hypogammaglobulinemic patients. It is presumably an antibody but none of those we have tested for. We did not test for antibodies against the diseases of clinical significance; these patients died most often from Staphylococcus aureus or pneumococci infections and not typhoid-paratyphoid fevers, tuberculosis, moniliasis or mumps.

By the use of immune electrophoresis, which allows greater qualitative analysis of serum protein, Grabar, Burtin and Seligmann [22] observed a deficiency of beta2 globulins in patients with agammaglobulinemia. This has been corroborated by Barandun, Huser and Hassig [20] who further reported that in the "antibody deficiency syndrome" these fractions were deficient independently of variations in the gamma globulin levels.

Two additional factors operative in chronic lymphatic leukemia which may decrease host resistance are inanition and treatment. With regard to the former, it has been observed that mass starvation does not invariably lead to infection [23]. Furthermore, Balch [24], in a study of a group of severely cachectic patients, and Bieler et al. [25], in a study of patients with anemia and hypoproteinemia, did not observe unusual susceptibility to infection or an immunologic deficit.

The form of therapy most often incriminated in decreasing resistance to infection is adrenocorticosteroids. While adrenocorticosteroids have been shown to diminish antibody production in animals [26-31], the results are extremely variable, depending on such factors as the antigen and species of the animals, the dose schedule of adrenocorticosteroids and its relationship to the time of administration of the antigen. The observations in man, using therapeutic levels of these hormones, are not consistent in defining the effects they may have on antibody production [32-35]. Although in general the net effect of adrenocorticosteroid administration is to decrease resistance to infection, there are situations in which the opposite is true [36,37]. One would have to define the infectious organism, whether the infection is acute or chronic, and the physiologic state of the host. The decreased resistance to infection may be accomplished by means other than decreasing antibody production, e.g., interfering with the inflammatory response. As is pointed out elsewhere [11], in each patient in group A the infectious complications preceded the administration of adrenocorticosteroids.

Radiation and alkylating agents are com-

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monly used for the treatment of chronic lymphatic leukemia. These agents also are used extensively in the treatment of inoperable carcinomas, especially of the lung, ovary and breast, and the adrenocorticosteroids are used in the treatment of inoperable mammary carcinomas. Except in special circumstances, such as treatment-induced agranulocytosis or exacerbation of inactive tuberculosis, one cannot regularly attribute infectious complications in these carcinomas to the use of these agents.

Hudson and Wilson [7] reported the average duration of chronic lymphatic leukemia in twenty-eight hypogammaglobulinemic patients to be 40.4 months and in twelve eugammaglobulinemic patients to be 21.8 months. They concluded that the incidence of hypogammaglobulinemia correlates best with the duration of disease. Ultmann et al. [9] reported that the mean duration of disease in their patients without hypogammaglobulinemia was 15.7 months compared to 35.2 months in those with a decrease in gamma globulin. This did not mean that hypogammaglobulinemia carried a favorable prognosis. Most of the patients with hypogammaglobulinemia had died and the complete duration of the disease was estimated, whereas most of the patients in the nonhypogammaglobulinemic group were alive and the complete duration of their disease could not be estimated. In our two groups of patients there was no significant difference between the hypo- and non-hypogammaglobulinemic groups in the mean duration of disease. In some patients in this study infectious complications developed very early and in others not until several years after the diagnosis had been established.

In no patient who was once hypogammaglobulinemic did gamma globulin levels return to normal. We agree with Creyssel et al. [8] that in patients with chronic lymphatic leukemia, hypogammaglobulinemia is a "signe permanent."

It is problematic whether hypogamma-globulinemia is a stage in the natural history of the disease or a characteristic feature of its initial presentation in some patients. Considering the wide variety of clinical, hematologic and serum protein findings, there may be more than one kind of chronic lymphatic leukemia despite the morphologic similarity of peripheral blood and marrow. For example, in the six years that observations have been made on the serum gamma globulin level in one patient

(J. D.), he has remained consistently hypogammaglobulinemic. In the three years that we have followed another patient (H. Ha.), his gamma globulin level has risen with the progression of his disease (from 1 to 6 gm. per cent of gamma globulin by serum electrophoresis). Either the disease starts de novo with leukemic transformation of the lymphatic system and the characteristic serum protein abnormality, or the disease evolves from a leukemic focus which progressively replaces normal lymphoid tissue. If chronic lymphatic leukemia starts with malignant transformation of a single cell and is diagnosed when the descendants of that cell are sufficiently numerous, we may be dealing with a clone of lymphocytes all having the same function or lack of function, with regard to protein synthesis, as the cell from which they were derived. Two populations of cells would be present, normal and malignant. If the leukemic lymphocytes were unable to synthesize gamma globulin, this would be clinically significant only when they replaced their normal counterparts to such an extent as to cause hypogammaglobulinemia. As clonal variants developed, other histologic or protein abnormalities might be evident. If leukemic lymphocytes destroyed the bone marrow or other vital organs before they had replaced all lymphoid tissue capable of gamma globulin formation, or if these leukemic cells produced gamma globulin, hypogammaglobulinemia would not occur. We have observed three patients and Ultmann et al. [9] have described a patient with chronic lymphatic leukemia whose serum gamma globulin level was normal at the onset of study but in whom hypogammaglobulinemia developed with progression of disease. These observations support the evolutionary or two-cell population concept of the development of hypogammaglobulinemia and suggest that the patient who initially presents with hypogammaglobulinemia had had asymptomatic leukemia until infection brought attention to the hematologic abnormality.

Craver [38] and Custer [39] have commented on the morphologic interrelationships of the lymphomas, and Osserman [40] has pointed out the overlap of serum protein abnormalities between the lymphoma and myeloma group of patients. The protein abnormalities add another dimension to the classification of disease of lymphoid origin. Further clinical correlation is necessary to determine the significance of the altered serum proteins for prognosis and therapy.

SUMMARY

Twenty-two patients with chronic lymphatic leukemia were studied clinically, hematologically and immunologically. The following immunologic tests were performed: serum electrophoresis, isohemagglutinins, response to typhoid-paratyphoid vaccination and to tuberculin, mumps and C. albicans skin tests, complement and properdin titers, and determination of serum macroglobulins.

The patients were divided into two groups according to their history of infectious disease. Patients with chronic lymphatic leukemia who had frequent infectious complications could, in general, be distinguished by their lower serum gamma globulin levels. None of the other parameters considered allowed us to differentiate between the two groups.

No relationship was found between duration of disease and hypogammaglobulinemia in this series, but there was some indication that hypogammaglobulinemia was a late stage in the natural history of chronic lymphatic leukemia.

The various serum protein abnormalities which may characterize patients with this disease suggest that despite morphologic similarities there may be more than one kind of chronic lymphatic leukemia.

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The Relationship of the Latex Fixation Test to the Clinical and Serologic Manifestations of Leprosy*

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Numerous studies have emphasized that positive serologic reactions, including those using globulin-coated latex particles, may be obtained in a variety of diseases other than rheumatoid arthritis, such as some of the rheumatic diseases [1–5], sarcoidosis [6], syphilis [7], liver disease [8] and leprosy [9]. Few reports, however, have attempted to study the possible clinical significance of these reactions in these other diseases. The present study was designed to determine whether or not the presence of this factor in the serum of patients with leprosy could be correlated with any differences in clinical manifestations or course of this disease.

MATERIAL AND METHODS

One hundred and one patients with leprosy were interviewed and examined at the U. S. Public Health Service Hospital, Carville, Louisiana. In selecting the cases, an effort was made to choose a group of subjects representing all stages of the disease.

In addition to careful review of each patient's history, physical examination, laboratory data and clinical course, particular attention was directed toward age, sex, descent, family history of illness, duration of disease, type of course, therapy and pathologic classification of each case, whether lepromatous or tuberculoid. In an attempt to assess activity of the disease, skin scrapings were studied for the presence or absence of leprosy bacilli. The extent of skin involvement and the degree of peripheral neuropathy were estimated in all cases. Skin involvement ranged between small infiltrated areas, with

positive skin scrapings, to involvement of nearly all the skin. Neurologic involvement ranged between a small patch of hypesthesia to motor and sensory neuropathy involving all four extremities. If digits had been lost as a complication of neurotropic bone disease, the total number of small bones missing from the hands and feet were noted.

Patients who had articular symptoms and signs were classified according to the proposed diagnostic criteria for rheumatoid arthritis [10]. Evidence concerning the presence of other diseases was carefully documented in each case. After review of the individual case histories, a profile was drawn indicating the type of course followed by each patient. These profiles were later classified into five groups (vide infra).

Routine laboratory investigations included determinations of blood hematocrit, serum concentrations of albumin and globulin, and blood non-protein nitrogen and urinalyses. Intravenous Congo red tests [11] and gingival biopsies were performed in all patients who exhibited albuminuria, azotemia or hepatosplenomegaly. Recent roentgenograms of the hands and feet of all subjects were examined and read by two of us (E. S. C. and R. C. W.) without prior knowledge of the clinical state. Special attention was focused on roentgenologic changes consistent with rheumatoid arthritis and neurotropic bone disease.

The latex fixation test [12] and the sensitized sheep red cell agglutination test [13] were performed on all serum samples. For the latter procedure the red cell suspensions were sensitized with equal volumes of rabbit antiserum containing half of the basic agglutinating titer. A quantitative precipitin test [14]

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was applied to twenty-three serum specimens which were known to give positive reactions by the latex fixation test. When serum samples were negative in the latex fixation test, the test was subsequently performed on an euglobulin fraction of the serum precipitated by the acid dilution method [15]. In the data to be presented, except when otherwise indicated, a patient was considered to exhibit a positive reaction in the latex fixation test when either whole serum or the euglobulin fraction thereof was positive. Serum was judged to be positive if the latex fixation test was positive in a final titer of 1:160 or greater [9]. The euglobulin fraction was considered to be positive if agglutination occurred in a dilution of 1:28 [12].

Adsorption Experiments. For these experiments lepromin (a boiled suspension of lepromatous tissue in physiologic saline solution) was obtained from Carville through the courtesy of Dr. George Fite. This material was rich in leprosy bacilli. Old tuberculin concentrated four times (Lederle) and standard cardiolipin indicator (Sylvania) were also used. Adsorption was carried out twice, both with lepromin and cardiolipin, by the addition of 0.1 ml. of each substance to 0.25 ml. aliquots of serum previously heated for thirty minutes at 56°c. The resulting mixtures were incubated at 38°c. for one hour and then centrifuged at 2,500 r.p.m. for five minutes. Adsorption with old tuberculin was performed with latex particles coated with old tuberculin. Old tuberculin, 0.1 ml., was added to 2 ml. of standard latex reactant solution, and 0.1 ml. of the resulting mixture was used to adsorb 0.25 ml. of serum. Adsorptions were performed in twenty latex-positive serum samples from patients with leprosy as well as in twenty serum samples from patients with rheumatoid arthritis who had titers from 1:320 to 1:5120 by the latex fixation test. After adsorption, the latex fixation test was again applied to these serum samples. The sheep cell agglutination test was performed in twelve serum specimens from patients with leprosy and twelve serum specimens from patients with rheumatoid arthritis both before and after adsorption with

Diffusion of lepromin in agar gel was studied, using Preer's modification [16] of the Oudin technic. Antigens against leprosy serum included concentrated old tuberculin and lepromin as well as heat-aggregated gamma globulin [17].

Serologic tests for syphilis were obtained in all patients. The serologic test for syphilis and the Kahn test were those described in the "Serologic Tests for Syphilis, 1955" manual [18] and were performed at the Public Health Service Hospital, Carville. The Treponema pallidum immobilization (TPI) test employed was that of Nelson and Diesendruck [19], with added complement [20] and increased sodium thioglycolate [21]. TPI tests were made on the serum samples of all patients with positive reactions to the serologic test for syphilis or the Kahn test.

TABLE I

RESULTS OF LATEX FIXATION AND SHEEP CELL
AGGLUTINATION TESTS IN SERUM OF ADULT PATIENTS
WITH RHEUMATOID ARTHRITIS AND IN PATIENTS
FROM THE MEDICAL OUT PATIENT DEPARTMENT OF
THE MASSACHUSETTS GENERAL HOSPITAL WITH
DISEASES OTHER THAN RHEUMATOID ARTHRITIS

	No. of	Patients	Per cent Positive	
Subjects	Latex Fixa- tion Test	Sheep Cell Agglu- tina- tion Test	Latex Fixa- tion Test	Sheep Cell Agglu- tina- tion Test
Rheumatoid arthritis	177	104	67.0	50.5
Non-rheumatoid con- trol	360	100	4.5	7.0

RESULTS

Results of the latex fixation tests on serum were positive in twenty-four of 101 patients with leprosy. When the same test was applied to the euglobulin fraction of the remaining seventyseven serum samples, twenty more showed agglutinating activity. Controls for the latex fixation test including serum samples from patients with rheumatoid arthritis and patients without articular disease are indicated in Table 1. No relationship between the duration of disease and the presence of a positive latex fixation test was noted when either whole serum or the euglobin fraction was used. (Fig. 1.) There was no relationship between the result of the latex fixation test and the patients' age, sex or race, or the presence or absence of a family history of leprosy, tuberculosis and rheumatoid arthritis.

An attempt was made to compare the incidence of positive reaction to the latex fixation tests and the clinical course of the disease. (Fig. 2.) In this figure, group A represents forty-six patients with constant unremitting leprosy of three or more years' duration. Group B consists of eight patients with active disease of more than three years but showing recent decline in the severity of the disease. Group C includes twelve patients who exhibited acute lepra reactions during three or more years. Group D consisted of ten such subjects who had leprosy less than three years, and group E included twenty-five patients in whom the disease

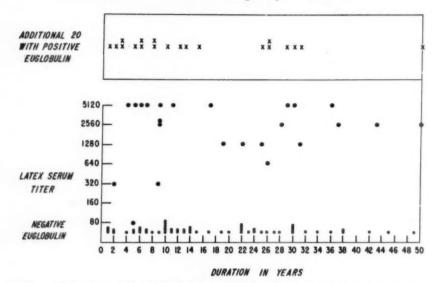


Fig. 1. This figure depicts the titer in the latex fixation test, using whole serum for 101 patients with leprosy, as related to the total duration of the disease. The upper portions of the figure indicate the added number of patients (with disease duration as indicated) who exhibited positive reactions in the euglobulin fraction. It will be seen that there is no relationship between the results of the latex fixation test and the duration of disease in leprosy.

was considered to have been arrested on the basis of the clinical manifestations, together with consistently negative smears for leprosy bacilli. There appeared to be no correlation between the results of the latex fixation test and the type of clinical course exhibited by the patients.

On clinical grounds, the patients were divided

COURSE OF DISEASE	NUMBER OF PATIENTS	POSITIVE SERUM LATEX	POSITIVE EUGLOBULIN LATEX	TOTAL
^	46	13	7	20
В	8	3	2	5
c	12	1	4	5
D SYEARS	10	1	4	5
E	25	6	3	9
TOTALS	101	24	20	44

Fig. 2. This figure depicts diagrammatically the types of clinical course exhibited by the 101 patients with leprosy. The number of patients displaying each type of course is shown, together with the incidence of positive reactions in the latex fixation test, using whole serum or the euglobulin fraction. No correlation could be made out between the type of course and the results of the serologic tests.

in accordance with clinical types. Eighty-eight patients were judged to be lepromatous, eleven were tuberculoid, and two exhibited a dimorphous or mixed lesion. The incidence of positive reactions to the latex fixation tests in the two main pathologic types is compared in Table II. There was no significant difference between the two groups. The severity of leprosy, whether assessed by degree of skin involvement or peripheral nerve damage, could not be correlated with the latex agglutinating factor or its titer, if positive.

Many disease entities other than leprosy also were present in the patients. (Table III.) Ten patients had had articular symptoms. This, together with the objective signs and x-ray appearance of the joints, warranted a diagnosis of probable or definite rheumatoid arthritis in

TABLE II
THE INCIDENCE OF POSITIVE REACTIONS TO THE
LATEX FIXATION TESTS (USING WHOLE SERUM OR
EUGLOBULIN FRACTION) IN TUBERCULOID AND
LEPROMATOUS LEPROSY

Type of Leprosy	No. of Patients	Positive Reactions	Per cent
Tuberculoid	1,1 88	4 39	36 44

three subjects. Eight patients had proved pulmonary tuberculosis, presently inactive, and fourteen patients had diabetes mellitus. Many patients gave a history of acquired syphilis; forty-four subjects had positive reactions to either the serologic test for syphilis or the Kahn test. If judged on the basis of positive reactions to the TPI tests, only ten patients had latent syphilis. Sixteen gave a past history of malaria. Seventeen had amyloidosis proved by histologic examination; an additional seven had probable amyloidosis as evidenced by a consistent clinical picture and serum Congo red retention of 30 per cent or less. Many patients were known to have several of these associated diseases; one, indeed, having all six.

It will be seen that the latex fixation test was more apt to give a positive reaction in patients whose leprosy was accompanied by one or more of these diseases than in those who had leprosy alone. The presence of multiple complications in many subjects made it difficult to determine, from these data, which of the associated diseases should be implicated as responsible for the increased incidence of positive reactions to the latex fixation tests. Therefore, patients with more than one diagnosis other than leprosy were excluded from this portion of the study. The results, thus modified, are depicted in Table IIIB It is apparent that, whereas only one of thirteen patients who had either diabetes or tuberculosis had a positive test result, the incidence of positive test results remained high in association with syphilis, malaria and amyloidosis. It must be emphasized that in forty patients with uncomplicated leprosy, 33 per cent had a positive reaction to the latex fixation test either in whole serum or using the euglobulin fraction. Using the sheep cell agglutination test, fourteen of the ninety-five serum samples examined gave positive reactions. This yields an incidence figure (15 per cent) which is somewhat lower than the incidence of positive reactions to latex fixation tests in these patients (24 per cent) when whole serum is employed.

The clinical diagnoses in the fourteen patients with leprosy who exhibited positive sheep cell reactions, and the results of the latex fixation test in these patients, are listed in Table IV. It will be noted that only half of these serum samples were positive by both serologic tests. (Of the seven serum samples which were negative in the latex fixation test, four were positive when the euglobulin fraction was employed.)

TABLE III

RELATIONSHIP OF POSITIVE REACTIONS TO THE LATEX
FIXATION TESTS (USING EITHER WHOLE SERUM OR
EUGLOBULIN FRACTION) TO THE PRESENCE OF
DISEASES OTHER THAN LEPROSY

A. Total Incidence

Disease		No. of	Patients	Reaction to Posi- tive Latex Fixation Tests		
	Defi- nite	Prob- able	Possi- ble	Total	No.	Per cent
Rheumatoid arthritis	2	1	7	10	7	70
Inactive tuber-	8			8	2	25
Diabetes History of	14			14	7	50
malaria			16	16	8	50
Positive TPI	10			10	7	70
Amyloid	17	7		24	13	54

B. Incidence Among Patients Whose Leprosy was Complicated by Only
One Other Disease

Disease	No. of	Positive Reactions to Latex Fixation Tests		
		No.	Per cent	
Rheumatoid arthritis	3	2	67	
Inactive tuberculosis	5	0	0	
Diabetes	8	1	12	
History of malaria	8	4	50	
Positive TPI	5	4	80	
Amyloid	14	7	50	
Leprosy alone	40	14	35	

No correlations could be made between the results of the sheep cell test and the clinical characteristics of the patients or their leprosy.

By prior adsorption with lepromin and old tuberculin it was possible to obtain negative reactions in seventeen of twenty serum samples which originally gave a positive reaction by the latex fixation test. (Table v.) Cardiolipin did not absorb the agglutinating factors in a similar fashion except in one instance. In control experiments, adsorption with lepromin, tuberculin or cardiolipin did not inhibit the ability of twenty serum specimens from patients with rheumatoid arthritis to react in the latex fixation test. On the other hand, all of ten serum samples which originally gave a positive reaction were rendered negative in the sheep cell agglutination test when adsorbed with lepromin. However, prior treatment with lepromin also rendered ten serum samples from rheumatoid patients negative when tested by the sheep cell agglutination technic.

TABLE IV

TITER IN SHEEP CELL AGGLUTINATION AND LATEX FIXATION TESTS, AND CLINICAL DIAGNOSES IN FOURTEEN PATIENTS WITH LEPROSY WHO EXHIBITED POSITIVE REACTIONS TO SHEEP CELL AGGLUTINATION TESTS

Case No.	Reciprocal Titer in Sheep Cell Agglutination Test	Reciprocal Titer in Latex Fixation Test	Diagnosis
2178	896	2,560	Leprosy, amyloid
2401	448	Positive in euglobulin	Leprosy, possible rheumatoid arthritis
2388	224	2,560	Leprosy
1785	224	1,280	Leprosy, possible rheumatoid arthritis, amyloid
2397	112	5,120	Leprosy, rheumatoid arthritis
2114	112	2,560	Leprosy, amyloid, diabetes, tuberculosis
2074	112	1,280	Leprosy, amyloid, diabetes
2425	112	320	Leprosy
2244	112	Negative	Leprosy
2313	112	Negative	Leprosy
1091	56	Positive in euglobulin	Leprosy, diabetes, malaria
1067	56	Positive in euglobulin	Leprosy, amyloid, malaria
2073	56	Positive in euglobulin	Leprosy
1562	56	Negative	Leprosy, amyloid, diabetes, tuberculosis, syphilis

Of twenty-three serum specimens which gave a positive reaction to the latex fixation test, sixteen formed precipitates against aggregated gamma globulin; the supernate, after centrifugation, had lost some of its ability to react in the latex fixation test as determined by a fall in titer.

With Oudin tubes, lines of precipitation were noted when serum from patients with leprosy was diffused against aggregated gamma globulin. The diffusion coefficient for the rings which were so formed was similar to that of control serum obtained from rheumatoid subjects tested concurrently in a similar manner.

COMMENTS

Clinical studies in rheumatoid arthritis have suggested probable relationships between the positive reactions obtained by the latex fixation test or the sensitized sheep red cell agglutination tests and the appearance of nodules [22], splenomegaly [23] and increased joint destruction [24]. Furthermore, several studies, both retrospective [25] and prospective [26,27], have suggested that the rheumatoid factor, when present early in the disease, has adverse prognostic significance. Although this suggestion might reflect a more virulent etiologic agent or deficit, it might, on the other hand,

	Adsorbed with Lepromin			l with Old erculin	Adsorbed with Cardiolipin	
Reaction	Serum from 20 Patients with Leprosy	Serum from 20 Patients with Rheumatoid Arthritis	Serum from 20 Patients with Leprosy	Serum from 20 Patients with Rheumatoid Arthritis	Serum from 20 Patients with Leprosy	Serum from 20 Patients with Rheumatoid Arthritis
Becomes negative	17	0 20	17	0 20	1 19	0 20

reflect a less favorable pattern of the host response.

If latex reactivity reflects host response, one would anticipate that patients with non-rheumatoid disease, such as leprosy, who exhibit this factor, might also exhibit a more severe form of their disease, and possibly follow a more scrious course. The data presented, however, indicate that there was no significant difference between the groups with positive and negative reactions to the latex fixation test with regard to the manifestations or course of leprosy.

The discovery that 15 per cent of the patients studied had positive reactions to sheep cell agglutination tests made careful scrutiny of all cases for underlying rheumatoid arthritis or other rheumatic diseases imperative. Other investigators have concluded that a positive reaction to the sheep cell agglutination test is highly specific for rheumatic diseases [28] and, in contradistinction to the latex fixation test, only rarely positive in other diseases including those associated with an increased amount of 19S gammaglobulins in the serum. In our study only one subject with a positive reaction to the sheep cell agglutination test had definite rheumatoid arthritis. Although two other patients exhibited findings that might be considered only as possible rheumatoid arthritis, the remaining thirteen patients had neither symptoms nor signs indicative of that disease. It might be pointed out that by utilizing the euglobulin fraction of serum for the sheep cell agglutination test [29], an even greater number of patients might exhibit rheumatoid factor specific for sheep cell sensitized with rabbit amboceptor. The marked disparity between the groups of patients with a positive reaction to the latex fixation test and the sheep cell agglutination test is consistent with recent observations that the factors responsible for agglutination of sensitized sheep cells and the latex fixation test are separate and distinct [30]. The difference in behavior between these two factors as described in the adsorption studies also favors this concept. However, the data do not support the theory that the sheep cell agglutination test is specific for rheumatic

In considering the incidence of a particular serologic test in leprosy, one must consider whether positive results reflect an abnormality due to the leprosy itself or merely to another complicating disease. This question is especially pertinent here because of the frequent occur-

rence of syphilis, amyloidosis, tuberculosis and diabetes among the patients studied. It must be emphasized, however, that 40 per cent of the 101 patients studied had leprosy alone, unaccompanied by another recognized chronic disease. In this group of forty patients there was a 33 per cent incidence of positive reactions to the latex fixation test, using either whole serum or the euglobulin fraction. The incidence of positive reactions was slightly higher in those cases in which the leprosy was associated with certain other diseases, namely, syphilis, amyloidosis and malaria. It was concluded, therefore, that the associated diseases observed in this study contributed, but only in part, to the total number of positive reactions.

We have demonstrated both by precipitin studies and by diffusion studies in agar gel that serum from patients with leprosy contains a component which combines with suitably prepared human gamma globulin. In this respect, the component of leprosy serum is analogous to the rheumatoid factor. The ability of tuberculin and lepromin to adsorb the agglutinating factor, specific for globulin-coated latex particles, requires explanation. It may be that this inhibitory capacity of lepromin and tuberculin is due to gamma globulin present in the crude extracts of these substances; however, there was no inhibition of agglutinating activity by them in rheumatoid serum. The factor may behave in a manner similar to rheumatoid factor, which has a propensity for combining with antigen-antibody complexes of large molecular size [31]. Indeed, the fact that circulating antibodies to lepromin may be present in the serum of patients with leprosy has been reported by others [32]. Why lepromin or tuberculin inhibits sheep cell agglutination in control serum from rheumatoid subjects is not readily apparent.

It is well known that serum from patients with leprosy may exhibit serologic reactions which are usually considered characteristic of other diseases. Examples are the serologic tests for syphilis [33], and the Middlebrook-Dubos test [34,35]. Except in isolated instances, however, the serologic tests currently in use, whether involving cardiolipin or tuberculin, lack substantial value as specific diagnostic tools. These methods are not precise enough to be correlated with severity, course or prognosis in an individual case of leprosy [36]. It would be of interest to compare our findings in the Carville group with tests performed on an entirely different popula-

tion of patients with leprosy who displayed a preponderance of the tuberculoid type, since the majority of these studied at Carville had

lepromatous disease.

It was apparent that the latex fixation test and the sheep cell agglutination tests as performed in this study share the same degree of non-specificity for the clinical manifestations of leprosy as do the serologic tests for syphilis and the Middlebrook-Dubos test.

SUMMARY AND CONCLUSIONS

Forty-four positive reactions to the latex fixation tests were obtained in the serum of 101 leprosy patients, twenty-four using whole serum and an additional twenty using the euglobulin fraction. The result of the sheep cell agglutination test was positive in fourteen of ninety-five of the same serum samples. Serologic studies suggest that the agglutinating factors in serum from patients with leprosy are similar if not identical to the so-called rheumatoid factors.

Duration, type of course and severity of leprosy appear to be unrelated to the presence of positive reactions to serologic tests. The incidence of other diseases found in association with leprosy has been recorded and their relationship to the latex fixation test and to the sheep cell agglutination test is discussed.

From the results of this study, it is not possible to define the significance of rheumatoid factors in serum from patients with leprosy. It is concluded that they probably play a non-specific role with respect to the clinical course.

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The Latex Fixation Test in Rheumatic Diseases*

A Review

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The purpose of the present review is to summarize results obtained with the latex particle fixation (FII L.P.) and sensitized sheep cell tests (S.S.C.) in rheumatic diseases and to appraise the FII latex particle test as a diagnostic tool. An attempt will be made to clarify further the mechanism of the latex fixation test. Ziff [1] has published a comprehensive review of serologic tests used in the diagnosis of rheumatoid arthritis and their clinical application. More recently, Bloch [2] reviewed the methodology and modifications of the latex fixation (FII L.P.) and bentonite flocculation test (B.F.T.).

SYSTEMS USED FOR DETECTING THE RHEUMATOID FACTORS

The underlying mechanism in serologic tests for rheumatoid arthritis involves a reaction between the rheumatoid factors present in the patient's serum and gamma globulin (the reactant) [3]. With the aid of an indicator or particulate carrier, i.e., red cells, latex, bentonite, this reaction is transformed into visible agglutination. Table I lists the agglutination and inhibition methods in current use. Serologic systems in which rheumatoid serum reacts with particulate carriers fall into two categories: (1) Immune sensitized systems, in which specific immune affinity for the particulate carrier is required—sensitized sheep cell (S.S.C.) [4,5], sensitized human D-erythrocyte (S.H.C.-D.) [10,11], human group O or A cells coated with rabbit antiserum to type O or A cells [18-20], sheep erythrocytes coated with the capsular

polysaccharide of Bacterium pneumoniae type B and sensitized with rabbit antiserum Bact. pneumoniae [20], alligator erythrocytes sensitized with rabbit antiserum [21], Brucella sensitized with incomplete brucella antibody [22], Streptococcal agglutination [16] and the Newcastle virus hemolysis [23]. (2) Non-immune sensitization by means of the non-specific adsorption of gamma globulin—FII coated tanned sheep cell (FII S.C.) [9], FII latex particle (FII L.P.) [12], bentonite flocculation (B.F.T.) [14] and FII collodion agglutination [24].

RHEUMATOID FACTORS

All human serum contains a group of high molecular weight proteins, macroglobulins. The main component has a sedimentation constant of 19S, corresponding to a molecular weight of about 1 million, and is made up of two different classes of proteins, alpha2 and gamma1 globulins [25]. Detection of the predominant macroglobulin species 19S, as well as of other macroglobulins, is possible by means of high speed ultracentrifugal analysis of serum or euglobin, by differential sucrose density ultracentrifugation, by precipitation with specific antibody to macroglobulins in gel-diffusion, by immunoelectrophoretic methods, and (only when present in large amounts) by free or paper electrophoresis. The immunologic activity of the 19S gamma₁ macroglobulins has been extensively studied [25,26]. They have a high carbohydrate content, show antigenic specificity, and exhibit cross

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Table 1
AGGLUTINATION AND INHIBITION METHODS FOR DETECTION OF RHEUMATOID FACTORS

Indicator or Carrier	Reactant	RF	Test	Abbreviations*
Sheep erythrocytes	Rabbit anti-sheep erythrocyte serum	Inactivated but not hetero- phil absorbed rheumatoid serum	Differential sheep cell	D.S.C.[4]
Sheep erythrocytes	Same as D.S.C.	Inactivated and heterophil	Heterophil absorbed sheep cell	S.S.C.[5]
Sheep erythrocytes	Same as D.S.C.	Euglobulin prepared from inactivated absorbed serum [6-8]	Euglobulin sheep cell	Eu.S.C.[6,7]
(a) Sheep erythrocytes (b) Known positive	(a) Rabbit antisheep erythrocyte serum [6] (b) Euglobulin as for	Euglobulin as for Eu.S.C.[6]	Euglobulin inhibi- tion	Eu.S.CI.[6]
rheumatoid serum	Eu.S.C.			
Sheep erythrocytes treated with tannic acid	Fraction II of pooled human serum	Inactivated and heterophil absorbed serum	FII coated tanned sheep cell	FII S.C.[9]
Human Rh-O positive erythrocytes	Human anti-D serum	Inactivated serum	Sensitized human D erythrocyte test	S.H.CD.[10,11]
Polystyrene latex par- ticles	Fraction II of pooled human serum	Not necessary serum inactivation	FII latex particle test	FII L.P.[12]
(a) Polystyrene latex particles		Euglobulin fraction	FII latex particle in- hibition [13]	
(b) Known positive rheumatoid serum	(b) Euglobulin frac- tion			
Bentonite particles	Fraction II	Inactivated serum	FII bentonite floccu- lation test	B.F.T.[14]
Streptococci	Streptococcal agglu- tinating factors ¹⁵	Inactivated serum	Streptococcal agglu- tination [16]	

^{*} Abbreviations for these systems, suggested at the First Conference on Serologic Reactions of Rheumatoid Arthritis in 1957 [17].

reactivity with other macroglobulins [25,26]. These substances appear to be composed of six 7S gamma globulin units covalently linked by disulfide bonds. Treatment of serum containing 19S material with sulfhydryl compounds, such as mercaptoethanol, glutathione or bisulfite, completely destroys this biological activity [25].

Certain macroglobulins present in serum of patients with rheumatoid arthritis, and to a lesser extent in serum of patients with other disorders [140], differ from the 19S macroglobulins of normal serum in their ability to react with gamma globulin in precipitation and agglutination reactions [27–33]. Two of these macroglobulins have been demonstrated by serologic technics, one reacting with both human and rabbit gamma globulin and the other with human gamma globulin alone [30,31,34]. The FII latex test demonstrates the presence of either of these macroglobulins. The sensitized sheep cell test, on the other hand, demonstrates only the presence of the one macroglobulin,

that react solely with rabbit gamma globulin. This may account for some of the differences in results obtained in studying various pathologic conditions by means of these two serologic technics [137,139].

A number of macroglobulins, collectively called "rheumatoid factors," have been demonstrated in serum by ultracentrifugation [30,31, 35–40]. A 22S component may be encountered in about one-third of serum specimens from patients with rheumatoid arthritis showing high agglutination titers [27]. The presence of 17S and 27S components has also been described [35]. Tests for rheumatoid factor, therefore, merely reflect the presence in serum of various macroglobulins which are reactive with other gamma globulin components.

The presence of such "rheumatoid factors" has been demonstrated in the plasma cells of synovial tissue and lymph nodes of patients with rheumatoid arthritis [41,42]. Serum from patients with sarcoidosis, cirrhosis, syphilis and other

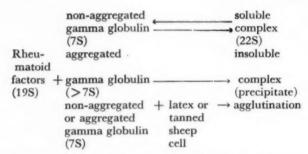


Fig. 1. Scheme to demonstrate serloogic reactions in rheumatoid arthritis (modified from Christian [29]).

conditions may contain similar macroglobulins. The nature of the serum response and the significance of the rheumatoid factor in rheumatoid arthritis and in other connective tissue disorders is difficult to interpret since it is not yet known whether the presence of rheumatoid factor is the result of an immunologic reaction related to the disease, rheumatoid arthritis, or whether it represents a more non-specific manifestation of host reactivity [30,32,33,37,38,43–50].

GAMMA GLOBULIN AS THE "REACTANT"

Figure 1 illustrates the mechanism of serologic reactions as suggested by Christian [29]. In precipitation and agglutination tests the serum reacts only with gamma globulin and not with other plasma protein components [3,9].

The main component of both normal and rheumatoid gamma globulins has an S20 value of 7 and a molecular weight of 160,000. 7S human gamma globulin isolated by electrophoresis or ultracentrifugation reacts very weakly or not at all in precipitation tests [27,28]. However, when 7S human gamma globulin is heated or modified by procedures which result in molecular aggregation, precipitation with rheumatoid factor readily occurs. Aggregates of human gamma globulin are essential for the sensitization of tanned sheep cells [20,27,28,51]. On the other hand, both 7S human gamma globulin and aggregated gamma globulin can sensitize latex particles [63]. In some serum from patients with rheumatoid arthritis a 22S component has been detected [27]. This material may represent the formation of a soluble complex consisting of 7S human gamma globulin and the 19S rheumatoid factor component [27].

Precipitation curves obtained with the same rheumatoid serum may vary, depending on the human gamma globulin sample used. The form of these curves ranges from the bell-shaped precipitin type to the flocculation type in which the precipitin continues far into the zone of antigen excess [29,51,52]. This may reflect differences in the amount and reactivity of aggregated gamma globulin in whole human gamma globulin preparations. Rheumatoid serum precipitation has recently been discussed by Vaughan [32].

THE LATEX PARTICLE SYSTEM

Such biological particles as sheep or human erythrocytes or streptococci, as well as such inert particles as collodion, latex and bentonite, are widely used as indicators for serologic reactions. The reactant is adsorbed onto the surface of the particle, and the carrier may then agglutinate or flocculate in the presence of rheumatoid factors to yield visible evidence of reaction. Latex particles were first utilized in the serologic reactions for rheumatoid arthritis in 1956 [12]. When vinyl monomers are dispersed in water and polymerized by a suitable free radical forming catalyst, small spheres of polymers are produced as a colloidal suspension in water. These spheres are called latex particles. The particles are emulsified in water with the aid of a chemical emulsifier. Monodispersed latex particles of uniform diameter ranging from 0.1 to 1.2 μ have been prepared by the Dow Chemical Company [53]. In their dispersed phase in aqueous solution they are negatively charged and seem to behave as lyophobic colloids. Their stability is determined by their charge and the charge of the surrounding medium. Latex particles with a diameter of 0.8 to 1.1 µ have been found most appropriate for serologic tests for the detection of rheumatoid factor. These particles are also presently used in serologic tests for histoplasmosis [54], lupus erythematosus [55-57], trichinosis [58], in the detection of C-reactive protein [60], antibodies to human heart tissue [61], thyroid autoantibody and for the quantitative determination of gamma globulin in hypogammaglobulinemia. In the serologic test for rheumatoid factor, latex particles are sensitized by pooled FII (gamma globulin) or by the patient's own serum gamma globulin.

For use in the routine FII L.P. test, concentrated latex particles of $0.81~\mu$ diameter (27.62 gm. per cent solids) are diluted twenty-one times to give the stock latex solution. One-tenth milliliter of the stock latex and 0.5~ml. of a 1 per cent FII solution are added to 9.4~ml. of glycine saline buffer solution, pH 8.2. This mixture represents the working solution for the FII

L.P. test. The concentration of latex in the working solution is therefore 0.13 mg. per ml. Since the density of latex particles is 1.06 [53] it may be estimated that this weight corresponds to 4.53 × 108 latex particles per ml. This represents a total surface area of 9.2 sq. cm. The added gamma globulin is adsorbed to the surface of the latex particles [62]. It has been estimated that a surface area of 9.2 sq. cm. will adsorb a maximum of 1.46 µgN human gamma globulin [62,63]. A latex particle of 0.81 μ diameter can adsorb a maximum of about 75,000 molecules of gamma globulin on its surface [63].

The present technic of performing the FII L.P. test provides an excess of more than 90 per cent of the gamma globulin remaining in solution [63]. This material includes both 7S and aggregated material. Since the aggregated gamma globulin reacts with rheumatoid factor in solution, the presence of an excess of this material may decrease the titer of latex particle agglutination. In the range of 10 to 100 μgN per ml. of pooled human gamma globulin, the end point of sixteen commercial preparations was found to be the same. When larger concentrations of human gamma globulin were used, however, differences became apparent which were most likely due to the varying amounts of aggregated material present [63]. An excess of 7S material, which does not react spontaneously with rheumatoid factors, has no effect on the FII L.P. titer. Since gamma globulins tend to aggregate spontaneously on standing, there may be variations in end point when the same bottle is used at different times. As a practical point, it is advised not to use the material from the bottom of the gamma globulin vial.

The important serologic property of aggregated human gamma globulin is its ability to react with rheumatoid factor and to neutralize it so that it is no longer reactive with a sensitized particulate carrier system, e.g., FII L.P., FII S.C., SHC-D. This fact may be utilized in a serologic inhibition procedure in detecting differences in reactivity of various FII preparations [69]. Differences in inhibiting capacity reflect differences in the amount and reactivity of aggregated gamma globulin present in these

FII preparations.

Various human gamma globulin fractions obtained by anion exchange cellulose chromatography sensitize latex particles equally [64]. Rabbit, pig, dog, cow, horse, cat or guinea pig gamma globulin can be substituted for human

gamma globulin in the latex fixation test [65]. and a routine method using porcine gamma globulin for latex particles has been developed [66]. The patient's own gamma globulin may serve as a sensitizing agent for the latex particles [67,68]. Latex particles coated with certain polysaccharides, or with heparin, will also agglutinate in the presence of rheumatoid serum [70,71]. However, a high incidence of positive results with serum containing elevated gamma globulin levels in patients with non-rheumatoid diseases limits the practical value of the heparin latex test [72]. Positive results of latex fixation tests in selected serum samples using heparin in place of human gamma globulin may be due to the simultaneous presence of endogenous gamma globulin [73].

In performing the FII L.P. test it has been observed that (1) some serum exhibits prozone phenomena [67,74-80]; (2) a large number of serum specimens react with latex particles in the absence of added human gamma globulin [87]; (3) the sensitivity of the test is increased by using the euglobulin fraction of the patient's serum [67]; and (4) an inhibition test can be performed

with the euglobulin fraction [13].

The prozone phenomenon has been variously ascribed to a thermolabile substance with the characteristics of serum complement [78,80] or to a gamma globulin inhibitor [82]. Artificial prozones may be induced in the FII L.P. test with purified rheumatoid factor or by the addition of alpha globulins [147]. In part at least, the prozone effect is due to the non-specific role of high concentrations of other serum proteins in the test system [83]. The prozone phenomenon can be abolished by allowing the serum to stand for a few days or by heating the serum to be tested at 56°c. for thirty minutes [78-80].

The enhanced sensitivity of the test when the euglobulin fraction of the patient's serum is used has been attributed to the removal of "inhibitors" present in whole serum. Two types of inhibitors have been demonstrated, one associated with human gamma globulin and the other with certain other proteins [65,68,84,85]. Gelatin and albumin, among others have been shown to reduce agglutination titers [65,85]. This has been ascribed to their protective colloidal action. That human and animal whole serum does not sensitize latex particles is probably due to the same mechanism [65,85].

Small amounts of gamma globulin cause latex

particles to flocculate whereas larger amounts increase the stability of the particles [63]. With the addition of large amounts of gamma globulin or other serum proteins, the particles assume a net charge and a surface due to adsorbed protein and are thereby stabilized [63]. Of the various plasma fractions it has been found that fraction V (albumin) or IV (a mixture of alpha and beta globulins) stabilize latex particles and thereby lower rheumatoid factor titers by a protective colloidal action [83]. Albumin is more effective than alpha or beta globulin in this respect [83]. The term "inhibitor" has been widely used to characterize the effect of protein upon serologic reactions in rheumatoid serum, but this term is somewhat misleading. It is more probable that serum protein fractions other than FII do not act as inhibitors but rather their primary effect in the latex system is that of stabilization through their protective colloidal action. The term "inhibitor" seems appropriate only in instances in which the rheumatoid factor is neutralized, as is the case with aggregated gamma globulin (thus preventing agglutination of sensitized carrier).

Sensitivity of the latex fixation test has been increased by a variety of modifications which include use of the euglobulin fraction of the patient's serum [13,75,77,86–90], a capillary tube [91], inhibition procedures [17,77,86,87] and slide

technics [89,92,144,147-158].

Eosin [89,92] and RA (Hyland) slide tests [144,147–158] are valuable as screening methods for the detection of negative or strongly positive sera. Weak or 1 plus slide test agglutinations should be checked by the tube method.

RESULTS WITH THE FII LATEX PARTICLES IN RHEUMATIC DISEASES AND IN CONTROL SUBJECTS

The introduction of tests for the detection of rheumatoid factor has not only provided a valuable aid in the diagnosis of rheumatoid arthritis but has also stimulated a great deal of research activity. The occurrence of "rheumatoid factors" in some but not in other rheumatic diseases raises the possibility that serologic methods might be of value in the classification of these conditions. However, the immunologic mechanism associated with the production of the factor needs further clarification.

Table II shows the incidence of positive test results in 3,080 patients with clinically diagnosed rheumatoid arthritis. The investigations included in the table showed positive results

with the FII L.P. method in 53 to 94 per cent (mean 75.8 per cent) of patients with rheumatoid arthritis. In 5,704 control subjects, including patients with rheumatic and non-rheumatic diseases, the test result was positive in 0 to 15.6 per cent (mean 5.2 per cent). Since this control group includes some patients with connective tissue disorders or other conditions in which high titer positive test results often occur, it does not represent a valid control group. The control groups in Table III represent healthy, randomly selected persons living in a particular community or employed at a hospital. The definite differences in these three groups (0.25, 0.74 and 1.4 per cent positive results) emphasize the difficulty in choosing reliable controls for determining the incidence of positive titers in a population, implying the importance of accurate epidemiologic information. All 3,981 non-rheumatoid patients, considered together, gave positive test results with a mean frequency of 0.80 per cent. An agglutination titer of 1:20 or greater was generally considered positive. Several authors, however, used dilutions of 1:40 to 1:160 as the lower limit for a positive test result, and there seemed to be no significant difference in the percentage of positive results obtained. The tests were performed without serum inactivation, and borate or glycine buffers were used. Variability in results observed in different laboratories can be accounted for in part by (1) the clinical material selected for study, (2) the use of gamma globulin preparations which vary in the amount of aggregates and other plasma fraction contaminants, and (3) the pH dependency of the method. A number of investigators have compared the results obtained on the same serum sample using the FII L.P. test with one or more technics: S.S.C. [66,85,88,92,95,97, 99,102,103,105,106,108,125,144,145], euglobulin FII L.P. [13,75,77,86-88,90,146], euglobulin inhibition FII L.P. [13,77,86,87], patient's own gamma globulin latex test [67], eosin slide test [89,122], slide test RA (Hyland) [89,125,126,129], modified Coombs' slide test [141], capillary precipitation test [122], capillary tube latex test [97], bentonite flocculation test [136] and streptococcal agglutination [105].

RESULTS WITH THE SENSITIZED SHEEP CELL
(S.S.C.) TEST IN RHEUMATIC DISEASES AND
IN CONTROL SUBJECTS

The incidence of positive test results with this procedure in 4,237 patients with rheumatoid

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TABLE II
RESULTS OF FII LATEX FIXATION TEST IN RHEUMATOID AND NON-RHEUMATOID CONTROL SUBJECTS

	Patients wi	ith Rheum	atoid	Control Subjects					
Author	Positive Titer - or >	No. of Patients	% Positive	No. of Patients*	% Positive	No. of Subjects†	% Positive		
Plotz and Singer [81]	20	150	71.3	1,160	2.7	200	1		
[74]	20	120	85.8	110	10.9				
Rothermick and Philips [93]	20	291	84.2	616	4.5				
Egghart, Widerman and Braunsteiner [94]	20	55	84.0	37	0				
and Lamont-Havers [95]	20	105	72.3	135	3.0	66	1.5		
Gofton, Thomas and Robinson [70]	20	71	83.0	166	11.1	75	3		
Meisels and Porush [79]	20	80	58.5	225	5.8	801	0.25		
Olsen and Rantz [95]	20	41	56.0	29	0	8	0		
Bartfeld, Mahood and Hartung [97]	160	75	68.2	46	4.3				
Hall, Mednis and Bayles [13] Pike, Sulkin, Coggeshall and Schultze	20	177	72.3	189	4.9				
[98]	20	165	69.7	115	5.2				
Valkenberg and de Mos [76] Berkowitz, Finkelstein, Corcos, Stein-	20	337	84.0	461	15.6	225	3.1		
brocker and Luce [99]	640	133	69.1						
Burby and Behr [66]	20	46	80.4	84	1.2				
Vaughn, Broome and Howell [100] Braunsteiner, Egghart, Reinhardt		100	83.0	200	3.0		• • •		
and Widerman [101]	20	184	94.4	218	3.6	27	0		
and Bryan [102]	20	140	64.0	52	3.8				
Petrini, Visconti and Grassi [103] Ulloa, Griffin, Hayes and Holley	20	30	70.0	376	4.3		• • •		
[104]	20	85	88.0	72	4.1	5	0		
Harter [105]	20	77	90.0	163	4.3				
Cechi and Ferrari [106]	20	54	70.1	55	1.8				
Cobb, Lincoln and Lincoln [107]	20					2,300	0.73		
Schubart, Cohen and Calkins [77]	160	183	52.9	343	3.5				
effrey [86]	160	76	71.0	166	3.6	48	0		
Dressner and Trombly [87] Egghart, Widerman and Braun-	160	137	62.0	525	3.6	48	0		
steiner [94]	160	68	88.2	118	1.6	30	0		
Hedberg [88]	20	38	73.7	43	0				

* Patients with both rheumatic and non-rheumatic disease and related conditions.

† Normal persons.

disease (Table IV) was 63.65 per cent. The control group, which included patients with rheumatic and non-rheumatic diseases as well as healthy persons, showed a 4.18 per cent incidence of positive reactions. Of a normal random sample control of 1,165 subjects, 5.67 per cent yielded positive results. In Ziff's review of the literature [1] positive results in rheumatoid subjects ranged from 30 to 100 per cent. This extreme variability may be explained on the

basis of differences in clinical sampling and by variability of laboratory technics, such as (1) use of cells from several animals, (2) method of adsorbing heterophil antibodies, (3) concentration of red cells, (4) titer and degree of agglutination obtained with the amboceptor, (5) quantity of the amboceptor necessary for optimum sensitization expressed in either agglutinating or hemolytic titers, (6) method of reading the tubes, i.e., by agglutination or

TABLE III

RESULTS OF FII LATEX FIXATION TEST IN PATIENTS WITH RHEUMATIC DISEASES AND CONTROL SUBJECTS

Data	References	Subjects	Positive		
	Total	(no.)	No.	%	
Clinical rheumatoid arthritis					
Adult	70,74–77,81,86,87,88,93– 106,108	3,018	2,284	75.67	
JuvenileRheumatoid-like diseases	13,75,77,86,101	51	6	11.8	
Psoriasis and arthritis	13,75,76,93,97,101,106	67	7	10.4	
	13,66,75,77,88,96,106	14	1		
	66,70,74,75,77,86,87,88, 93,95,96,98,104,105,106	195	5	2.6	
Diseases possibly related to rheumatoid arthritis					
Systemic lupus erythematosus	13,66,70,75,76,77,80,84, 86,87,89,91,92,93	161	33	20.5	
Scleroderma		23	4	17.4	
Dermatomyositis and polymyositis		16	5		
Periarteritis nodosa		9	2		
Rheumatic fever		451	12	2.7	
Non-rheumatoid arthritis					
Osteoarthritis		757	15	2.0	
Infectious arthritis		22	0		
Gout		115	2	1.7	
Non-arthritic rheumatic disease					
Fibrositis	13,66,74,93,97,98	206	8	3.9	
Bursitis		17	1		
Control subjects	-				
Healthy persons	96	801	2	0.25	
Community study		2,300	17	0.74	
Apparently healthy hospital population	63,70,75,76,81,86,87,104, 108	880	13	1.5	

pattern, and (7) the level chosen for a positive test result, which remains to some extent a matter of individual choice. Borderline titers of 1:32 or 1:64 may present difficulties in interpretation.

RESULTS WITH THE FII L.P. AND S.S.C. TESTS IN SOME RHEUMATOID AND NON-RHEUMATOID ARTHRITIDES (TABLES III AND IV)

Juvenile Rheumatoid Arthritis. In seventy-five children with rheumatoid arthritis an incidence of 11.8 per cent was found with the FII L.P. as opposed to 25.7 per cent using the S.S.C. The low incidence of positive results with both procedures may be due either to a lack of sensitivity of the tests or, more likely, to the failure of children to develop macroglobulins in significant titer.

Rheumatoid Factor Unaccompanied by Peripheral Joint Changes. In 428 cervical roentgenograms from a random sample population, 13 per cent showed roentgenologic changes compatible with rheumatoid arthritis [124]. No correlation with the clinical diagnosis of rheumatoid arthritis was noted in these cases. However, a relationship did exist between a positive sheep cell agglutination and roentgenologic grading for rheumatoid arthritis in the cervical spine [124]. The discovery of rheumatoid factor has led, in recent years, to increased investigation of the possible hereditary or environmental nature of rheumatoid arthritis [127-131]. Comparative studies on the incidence of rheumatoid arthritis in rural as well as urban populations [96,107, 121,124] have shown that rheumatoid factor (by agglutination and inhibition technics) may

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TABLE IV

RESULTS OF SENSITIZED SHEEP CELL AGGLUTINATION TEST IN PATIENTS WITH RHEUMATIC DISEASES AND CONTROL SUBJECTS

P	D. 4	Subjects	Positive		
Data	References	(no.)	No.	%	
Clinical rheumatoid arthritis					
Adult	1,46,110-115	4,237	2,697	63.65	
Juvenile	1,110,111	226	58	25.7	
Rheumatoid-like diseases					
Psoriasis and arthritis	1,46,111,115,116	625	86	13.8	
Reiter's disease	1,111,115	114	19	16.7	
Arthritis associated with ulcerative colitis	1,117,118,119	71	5	7.0	
Ankylosing spondylitis	1,46,111,115,120	1,526	75	4.9	
Diseases possibly related to rheumatoid arthritis					
Systemic lupus erythematosus	1,46,111,114,115	212	83	39.2	
Scleroderma		82	28	34.1	
Dermatomyositis and polymyositis		22	5	22.7	
Periarteritis nodosa	1,46,111,114,115	58	9	15.5	
Rheumatic fever	1,46,111	885	30	3.4	
Non-rheumatoid arthritis					
Osteoarthritis	1,111,115	884	52	5.9	
Infectious arthritis	1,115	71	2	2.8	
Gout	1,111,115	217	5	1.9	
Control subjects					
Community studies	121	1,165	66	5.67	

occur in subjects taken at random. Most of these subjects with a positive reaction showed no evidence of roentgenologic joint involvement or other clinical evidence of rheumatoid arthritis [127,128].

Rheumatoid Factor in "Variants" of Rheumatoid Arthritis. Ankylosing spondylitis, considered by some to be a variant of rheumatoid arthritis, shows a positive FII L.P. and S.S.C. reaction in 2.6 to 4.9 per cent of cases. This is similar to the incidence of positive results encountered in the normal population with the two methods. In psoriatic arthritis results of the FII L.P. and S.S.C. tests are positive in 10.4 per cent and 13.8 per cent of cases. A relationship between ankylosing spondylitis and psoriatic arthritis on the one hand, and rheumatoid arthritis on the other is debatable [1,116,120,133,135]. Using the S.S.C. tests, positive results were obtained in 16.7 per cent of patients with Reiter's syndrome. Negative findings were observed with the FII L.P., but this was in a small sample. A large number of patients with uveitis or iritis have been studied in an effort to discover a possible association with rheumatoid arthritis [96,134]. Of twenty-eight patients thus afflicted, only one showed a positive

reaction with the FII L.P. test in the absence of clinical rheumatoid arthritis [96]. The S.S.C. test in 190 such cases revealed an incidence of positivity of 5.26 per cent [134].

Rheumatoid Factor in Non-rheumatoid Diseases. An incidence of positive FII L.P. and S.S.C. tests comparable to that of the normal population was found in patients with osteoarthritis, infectious arthritis, fibrositis, bursitis and gout.

Rheumatoid Factor in Other Connective Tissue Disorders. With the exception of rheumatic fever, a high incidence of positive test results by both methods occurs among the connective tissue diseases. These conditions present overlapping symptoms and frequently manifest evidences of an altered immunologic response. FII L.P. and S.S.C. tests were positive in 20.5 and 39.2 per cent, respectively, of patients with systemic lupus erythematosus, scleroderma, dermatomyositis, polymyositis and polyarteritis nodosa, all diseases involving connective tissue.

Rheumatoid Factor in Non-arthritic Diseases. "Rheumatoid factors," as detected by serologic technics, are clearly not specific for rheumatoid arthritis. Positive titers have been encountered in serum from patients with sarcoidosis [137],

syphilis [139], kala-azar [137], cirrhosis of the liver [1,87,137,138], hepatitis [1,87,138], lymphomas [70], and viral infections [87]. However, titers observed in these conditions are generally low, and positive results frequently revert to negative when the activity of the disease subsides [87]. Furthermore, in some of these illnesses, e.g., syphilis and sarcoidosis, test results are frequently positive by the FII L.P. method, while results of the S.S.C. tests are more likely to remain negative [137,139]. Bartfeld [140] has recently reviewed the incidence and significance of seropositive tests for rheumatoid factors in non-rheumatoid disease.

COMMENTS

Serologic tests for rheumatoid arthritis detect certain macroglobulins collectively referred to as "rheumatoid factors." A latex fixation titer of 1:20 or greater is indicative of the presence of macroglobulins reactive with gamma globulin on the surface of a latex carrier particle. In general, high agglutination titers are encountered in active rheumatoid arthritis, but low titers not infrequently occur even in the presence of clinical activity. High titers may persist regardless of disease activity, erythrocyte sedimentation rate, stage of disease or effectiveness of therapy [1,32]. Frequently, very high titers are obtained in tests on patients with more advanced manifestations of the disease, i.e., subcutaneous nodules, x-ray changes or splenomegaly [1,32,75]. A positive test result in persons with non-rheumatoid diseases as well as in asymptomatic relatives of patients with rheumatoid arthritis or in related connective tissue disorders reflects the presence in the serum of macroglobulins which possess the serologic properties of rheumatoid factors. A positive serologic test result must always be correlated with clinical, pathologic and roentgenologic changes [123]. A negative test result does not rule out the diagnosis of rheumatoid arthritis.

Opinion is divided as to the classification of "variants" of rheumatoid arthritis such as juvenile rheumatoid arthritis, ankylosing spondylitis, psoriatic arthritis, Reiter's disease and arthritis accompanying other diseases such as ulcerative colitis [1,111,112,116,117,132,133,135]. In their recent analysis of these conditions, Mc-Ewen et al. [135] found that 96 per cent of patients with juvenile rheumatoid arthritis had a positive inhibition test result as compared to an incidence of 0 to 2.4 per cent among patients

with the other so-called variants. The inhibition test is generally considered to be the most sensitive technic for the detection of rheumatoid factor. Negative inhibition test results are usually found in serum of patients exhibiting "variants" of rheumatoid arthritis [1,6,13,87,135]. Probably these "variants" are either unrelated to rheumatoid arthritis or exhibit differences in elaboration of macroglobulins which separate them from rheumatoid arthritis on immunologic grounds.

The presence of macroglobulins in the serum in these disorders may represent either a quantitative increase in a specific component which normally occurs in small amounts [30], or the product of an abnormal cell possessing a distorted mechanism of protein synthesis [26], or an antibody, perhaps antibody against an antigen-antibody reaction [49]. Kunkel is of the opinion that systemic lupus erythematosus and rheumatoid arthritis are related [45] in that they represent different manifestations of a profound immunologic alteration. The main link between these diseases is the presence of rheumatoid macroglobulins in the serum of patients or of their blood relatives [45]. Absence of rheumatoid factor in cases of rheumatoid arthritis may reflect other immunologic alterations or deficiency of the immunologic mechanism. It may also be that delayed allergic response rather than classic immunity is responsible for certain forms of rheumatoid disease or related connective tissue disorders [47,48,50,142]. According to Pappenheimer, Scharff and Uhr [143] the antigenic binding site is fixed to the cell and is responsible for the reactivity associated with the delayed hypersensitive state. Antibody production would then be the second step in the development of immunologic reaction.

Further serologic investigations will undoubtedly add to our knowledge of the rheumatoid macroglobulins and may possibly elucidate either the specific host factors or the antibodies responsible for the hypersensitivity phenomena of arthritis and related connective tissue disorders.

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Clinicopathologic Conference

Abdominal Pain, Hyperpyrexia, Diabetic Ketoacidosis, Oliguria and Convulsions

STENOGRAPHIC reports, edited by Lillian Recant, M.D. and W. Stanley Hartroft, M.D. of weekly clinicopathologic conferences held in the Barnes and Wohl Hospitals, are published in each issue of the Journal. These conferences are participated in jointly by members of the Departments of Internal Medicine and Pathology of the Washington University School of Medicine and by Junior and Senior medical students.

This patient, a thirty-three year old white laborer from rural Missouri, was admitted to the Barnes Hospital for the first time on July 25, 1960; he died on August 6, 1960.

Except for occasional nocturia and questionable polydipsia, the patient was in good health until about three weeks before admission when an aching epigastric pain developed. The pain was intensified by the intake of food, but was not associated with nausea, vomiting or melena. He continued to work until six days prior to admission; his abdominal discomfort then increased markedly in intensity, and he became extremely weak while at work. After returning home, he complained of epigastric discomfort and vomited twice, his vomitus being described as yellow in color and without blood. His physician told him that he might have "ulcers" and gave him pills of unknown type. The pain and vomiting did not cease; the vomitus gradually turned dark brown in color. On July 22 he experienced sharp pain in the epigastrium and upper left quadrant, without radiation. He was given promazine and meperidine. The next morning the patient was taken to a hospital where he was found to be comatose, with 4 plus glycosuria and a blood sugar of 350 mg. per cent. Two hundred units of Lente insulin were administered over a six-hour period, and 300 units of regular insulin thereafter. However, his blood sugar continued to rise over the next twenty-four hours, reaching 1,200 mg. per cent. He remained comatose. He received 4,000 cc. of fluid intravenously, and his urine output was good. He was transferred to the Barnes Hospital forty-eight hours after being hospitalized.

The patient's mother and half-brother on the mother's side had diabetes mellitus. The patient was described as a moderate alcoholic, reportedly drinking up to twenty-four cans of beer per weekend. However, he had taken no alcohol for three weeks before admission.

On physical examination the rectal temperature was 41.5°c., pulse 160 per minute and regular, blood pressure 40/0 mm. Hg and respirations 40 per minute, somewhat irregular, deep and labored. The skin was flushed, dry and hot. The patient was well developed; his nutritional status was good. He was unresponsive and appeared to be somewhat dehydrated. Examination of the head, eyes, ears, nose and throat was within normal limits, except for moderate dehydration of the mucous membranes. The neck was supple; there was no enlargement of the lymph nodes. Breath sounds were diminished bilaterally posteriorly; a friction rub was heard over the lower lobe of the left lung posteriorly and fine scattered inspiratory rales were detected at the bases of both lungs. The heart was not enlarged; heart tones were fair; a grade 2/6 pulmonic systolic murmur was heard. Abdominal examination was non-contributory. Bowel sounds were decreased. A Foley catheter was in place. The patient was unresponsive, but was noted to move all extremities spontaneously. No deep tendon reflexes could be elicited. There were no abnormal reflexes.

Laboratory data were as follows: hemoglobin 15.1 gm. per cent, hematocrit 40 per cent, white blood cell count 8,600 per cu. mm. with a differential of 77 per cent polymorphonuclear leukocytes, 11 per cent band forms, 11 per cent lymphocytes and 1 per cent monocytes. Urinalysis showed a specific gravity of 1.019, pH 4.5, protein 3 plus, sugar 2 plus, acetone 4 plus. Microscopic examination of the centrifuged urinary sediment revealed 3 to 4 red blood cells per high power field. Stool guaiac reaction was

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trace. Serum acetone was 2 plus (undiluted). Serum bilirubin was less than 0.8 mg. per cent. Prothrombin time was 80 per cent of normal. The result of the direct Coombs' test was negative. (See Table I for additional laboratory data.)

Oxygen, vasopressor drugs, saline solution, sodium lactate, potassium and aqueous penicillin were administered; within five hours the patient was responsive and complaining of epigastric pain. Urine acetone had disappeared. The administration of vasopressor drugs was discontinued and the patient's blood pressure was maintained spontaneously at 160-130/80-70 mm. Hg. The administration of glucose solution, with regular insulin added, was started. A good urinary output continued. Two hours later the patient experienced generalized flaccid paralysis and the serum potassium level was found to be only 2 mEq. per L. More potassium was given; however, his blood pressure fell to 60/0 mm. Hg within two hours. The administration of oxygen and vasopressor agents was started again. After the intravenous administration of 440 mEq. of potassium, the patient's muscle strength was much improved. About five hours later, with continued improvement in muscle strength, the urinary output began to fall; within six hours it was virtually zero. At that time a creatinine urine:plasma ratio was determined and found to be 49. Urine osmolality was equal to 290 mOsm. per L. The patient's temperature remained elevated but was kept below 38.5°c. with tepid sponges. Blood, urine and throat cultures were negative. Chest roentgenograms revealed pneumonitis of the lingula, upper lobe of the right lung and lower lobe of the left lung, and a small left pleural effusion. A single roentgenogram of the abdomen was indeterminate. Twenty-six-hour urinary output up to 10 A.M. on July 27 was 400 cc. Treatment was continued with antibiotics, and adrenal cortical steroids were administered intramuscularly. Because of a rise in serum potassium, potassium exchange resins were administered rectally. The patient's blood pressure was maintained satisfactorily with the intravenous administration of vasopressor agents. Intravenous fluids were restricted to small volumes of 50 per cent glucose and water with added insulin.

On July 28 the hematocrit was 32 per cent and the white blood cell count was 13,750 per cu. mm. Urinalysis revealed 2 plus proteinuria and many casts, including granular, hyaline and red blood cell casts. Many yeast forms were also

seen in the centrifuged urine sediment. Stool guaiac reaction was 1 plus. Serum potassium ranged between 0.8 and 5.9 mEq. per L. Blood urea nitrogen was 74 mg. per cent. Because the patient was considered to be somewhat dehydrated, he was given 10 per cent glucose and water intravenously. The same day retrograde pyelography revealed a normal left collecting system and overdistention of the right collecting system with pyelolymphatic backflow. The patient's urine was strained repeatedly and what was thought to be tissue was obtained and sent for pathologic examination. This "tissue" proved to be clumps of yeast. When the patient appeared relatively well hydrated, the venous pressure was 150 mm. water. Since very small amounts of vasopressor drugs had been required to maintain his blood pressure, these were stopped and he was given no more until two days before death. During the day of July 28, urine volume was only 285 cc. The next morning the creatinine urine: plasma ratio was found to be approximately 14; urine sodium was 52 mEq. per L., serum sodium was 146 mEq. per L., serum potassium was 5.7 mEq. per L. and blood urea nitrogen was 96 mg. per cent. Chest roentgenograms revealed clearing of the previously described pneumonitis. The patient felt relatively well and strong. He continued to show clinical evidence of improvement. On July 31 he was allowed up into a chair. On August 2 the antistreptolysin-O titer was 100 units, serum complement level was 1:4 and urine osmolality was 332 mOsm. per L.

By August 3 the urinary output had increased to about 700 cc. per twenty-four hours. However, on that morning the patient complained of a severe frontal headache. Neurologic examination was unrevealing. He vomited approximately 75 cc. of clear greenish vomitus during the day. That night he began to have repeated generalized grand mal seizures. There were no localizing neurologic signs. Lumbar puncture revealed an initial pressure of 155 mm. water, final pressure 135 mm. water, after removal of 6 cc. of slightly xanthochromic cerebral spinal fluid. There were 5 cells per cu. mm. without acid. and 1 cell per cu. mm. with acid; cerebral spinal fluid protein was 256 mg. per cent, sugar 174 mg. per cent, chloride 127 mEq. per L. India ink preparation was negative. After nine generalized seizures and treatment with sodium amytal, phenobarbital and Dilantin,® the convulsions ceased. The patient still had no focal neurologic

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signs. It was believed that the convulsions were secondary to uremia, even though the blood urea nitrogen had leveled off between 100 and 120 mg. per cent. Extracorporeal dialysis was therefore attempted. However, after two hours of dialysis the patient's respirations suddenly ceased, he became hypotensive, and his right pupil became dilated and fixed. Administration of vasopressor agents was resumed and artificial respiration, through an endotracheal tube using intermittent positive pressure oxygen, was begun. Within a half hour both pupils were dilated; he was completely areflexic and hypotensive. The extracorporeal dialysis was discontinued and he was returned to the ward. His blood pressure was 150/115 mm. Hg with intravenous vasopressor solution running; pulse was 100 per minute and regular. Pupils remained dilated; there were scattered retinal hemorrhages and retinal edema. He remained comatose and completely areflexic. Lumbar puncture showed an initial pressure of 340 mm. water, final pressure was 270 mm. water, after removal of 4 cc. of slightly xanthochromic cerebral spinal fluid. There were 308 cells per cu. mm., described as fresh red blood cells. Although the patient's urinary output was fairly good, his condition deteriorated slowly and progressively the administration of more and more vasopressor agents was required to maintain his blood pressure. He died on the morning of August 6, 1960.

CLINICAL DISCUSSION

DR. CARL V. MOORE: The patient was a young man, only thirty-three years of age, when he became ill and died within a period of approximately five weeks. He had been a weekend beer drinker, but so far as we know had been in good health until early in July 1960. For several weeks he complained of an aching epigastric pain, intensified by eating, but he was able to continue working. Six days before he was admitted to the Barnes Hospital, the pain became more severe and he began to vomit. Melena and hematemesis were not recognized, although the vomitus apparently became dark in color. On July 22, the pain in the epigastrium and upper left quadrant was sharp, but it did not radiate. The following morning he became comatose and was taken to his local hospital. From this time on his course was a very complicated one. He was found to have diabetes, and was presumed to be in diabetic coma. Through

an error, he was first treated with Lente insulin, but was then given 300 units of regular insulin. Because his blood sugar continued to rise to levels as high as 1,200 mg. per cent, he was transferred here on July 25, still comatose, with a temperature of 41.5°c., in shock, and with manifestations of hypokalemia.

He responded to the administration of insulin. vasopressor drugs and unusually large amounts of potassium, but his originally good urinary output fell to very low levels within six hours. For the next ten days he was treated properly for acute renal failure. The problem of controlling the dosage of insulin and of antibiotics in a person who had practically no urinary output was a formidable one, expertly handled by the house staff. On August 2 and 3 a rather severe headache developed, but everyone was encouraged when his twenty-four-hour urinary output rose to 700 ml. That evening, however, he had nine grand mal seizures, at least some of which seemed to begin in his right arm. These were finally brought under control with the administration of rather large doses of barbiturate and Dilantin. The renal consultant decided that hemodialysis should be performed; the procedure, technically satisfactory, was stopped after two hours when the patient's spontaneous respirations ceased. His blood pressure dropped, first the right and then both pupils became dilated and unresponsive to light, scattered retinal hemorrhages and retinal edema appeared. Spinal fluid pressure was found to be 340 mm. water. The fluid was xanthochromic and contained 308 fresh red blood cells per cu. mm. Supportive therapy maintained life for nearly thirty-six additional hours, but he died on the morning of August 6.

In the interest of brevity, many details of the clinical record were omitted from the protocol. I should mention, however, that a spinal puncture was performed on the day the patient was admitted to the hospital. The opening pressure was 360 mm. water, the tap was traumatic, so that the fluid was initially bloody, but cleared after 1 or 2 cc. of fluid had been removed. The protein content was 58 mg. per cent.

Dr. McAlister will discuss the roentgenograms.

DR. WILLIAM H. MCALISTER: The chest roentgenogram taken on admission showed the bony structures to be normal. The cardiac size and configuration were normal, along with the pulmonary vascularity. The paratracheal and hilar lymph nodes were enlarged and contained

calcium. Infiltrates were present in the upper lobe of the left lung and lower lobes of both lungs. A moderate-sized left pleural effusion was present, along with a minimal right pleural effusion. A chest roentgenogram taken three days later showed some clearing of the infiltrates. The left pleural effusion was, in part, loculated. A chest roentgenogram taken nine days after admission showed an increase in the parenchymal disease and pleural fluid in the lower lobes.

On the plain roentgenograms of the abdomen, the bony structures were normal except for what appeared to be a calcified enchondroma in the left ilium. The liver and spleen were not enlarged. No vas deferens, pancreatic or vascular calcifications were seen. The right psoas shadow was identified, while the left was only partially seen. The kidneys were smooth and of normal size. Bilateral retrograde pyelograms showed that the left collecting system was normal. On the right there was pyelolymphatic and sinovenous backflow, related to the pressure of the injection.

DR. MOORE: Dr. Gieselman, I failed to mention that this man continued to have epigastric pain throughout his hospital course. Our information about the nature of the gastrointestinal lesion or the cause of his epigastric pain is scanty. Would you discuss the differential diagnosis and indicate the most likely possibilities?

Dr. RALPH GIESELMAN: One has to decide whether the abdominal pain was a manifestation of a systemic disease process, or caused by a primary lesion within the abdominal cavity. Abdominal pain or epigastric distress is not an uncommon manifestation of uremia. Abdominal discomfort of varying kinds often precedes the clinical diagnosis of diabetic ketoacidosis, but usually not for three weeks as occurred in this man. The left-sided pneumonia may have accounted for the episode of pain in the upper left quadrant that was described separately from the original pain. We are handicapped by not knowing whether this pain was associated with fever. Intracranial disease and polyarteritis should also be mentioned as possibilities. We are told that the patient's abdomen was not tender and that no masses were felt. Early in the course of his illness, infectious hepatitis and pancreatitis were possible diagnoses, but the subsequent clinical course makes both seem unlikely. In particular, the initial symptoms were too insidious and the course too prolonged for acute

hemorrhagic pancreatitis. The pain does not suggest classic peptic ulcer as was diagnosed elsewhere.

DR. MOORE: Dr. Shatz, do you agree with Dr. Gieselman that pancreatitis is an unlikely diagnosis? Would you also comment about the possibility that acute gastritis, produced by excess alcohol, might cause this kind of discomfort?

DR. Burton A. Shatz: This patient had a history of alcoholism and had upper abdominal pain followed by hyperglycemia and diabetic coma. This chain of events one associates with severe hemorrhagic pancreatitis, but the absence of the physical findings of peritoneal irritation is disturbing. Perhaps the signs were masked because he was comatose.

DR. MOORE: Even after he came out of coma he did not have a board-like abdomen or particular abdominal tenderness.

Dr. Shatz: Gastritis would not likely produce this picture unless there was an associated ulceration. Duodenal ulcer with posterior penetration might produce the abdominal manifestations, but hemorrhagic pancreatitis is still attractive to me as a diagnosis in this patient. The subsequent course could well be explained by hemorrhagic pancreatitis with marked loss in circulating fluid volume as a result of the inflammatory process around the pancreas, causing transudation of fluid into the retroperitoneal space; this could produce the shock and secondary oliguria. Also, the sudden severe diabetes could be explained on this basis, and even, perhaps, the left pleural effusion. Normal serum diastase levels can occur in severe pancreatitis; furthermore, the determinations were made at a time when an elevated level could well have returned to normal.

DR. Moore: Dr. Daughaday, is there anything strange about the appearance of coma when the blood sugar was only 350 mg. per cent? Would you also comment about the subsequent rise in the blood sugar to levels of 1,200 mg. per cent, despite the administration of several hundred units of Lente insulin and 300 units of regular insulin?

DR. WILLIAM H. DAUGHADAY: Excluding extraordinarily high blood sugars, there is no correlation between the mental state and the blood sugar value. The very high blood sugar level is of interest. In my opinion, this never develops in the presence of good renal function. It implies a functional if not an organic renal defect. Normally, when the blood sugar level

starts to rise there is a tremendous increase in renal excretion, which acts as a safety valve and keeps the blood sugar below the range of 800 or 900 mg. per cent. In most cases of diabetic acidosis, patients whose blood glucose levels rise to 900 to 1,200 mg. per cent or higher probably are unable to excrete glucose; this complicates the other disturbances of carbohydrate metabolism. I would suspect that this patient was having circulatory trouble at the time he had a blood sugar level of 1,200 mg. per cent.

DR. MOORE: Dr. Kipnis, the carbon dioxide of 28.5 mEq. per L. was surprising in a man thought to have diabetic acidosis. The degree of hypokalemia was also quite unusual.

DR. DAVID KIPNIS: Unfortunately, we do not know what intravenous fluid therapy he received before his transfer here. The normal plasma carbon dioxide content suggests that he probably received some form of alkalinizing solution. The finding on admission of a high blood sugar with acetone bodies in serum and urine indicates that this patient had diabetic ketosis. I first saw him about twenty-four hours after his arrival on our wards; at that time the major problems were those related to severe hypokalemia and the maintenance of a normal blood pressure. The family informed the house staff that he experienced a severe gastrointestinal upset several weeks previously and had vomited intermittently and not eaten since that time. Under these circumstances, severe potassium depletion would be expected and it is of note that the house staff, being well aware of this complication, initiated potassium therapy soon after his arrival. The hypokalemia resulting from total body potassium depletion was probably worsened by the glucose-insulin infusions required in the therapy of his diabetic ketosis. In the face of considerable intravenous potassium therapy, a rapidly progressive ascending paralysis developed. For this reason, more rigorous potassium replacement therapy was recommended and he received in excess of 450 mEq. in less than twenty-four hours, with resolution of his paralysis, but the plasma level rose only to the range of 2.5 to 2.7 mEq. per L. At the time of this rigorous replacement regimen and the continued administration of insulin, his blood sugar dropped to levels of about 200 mg. per cent and coincidentally the patient became oliguric.

DR. MOORE: Why do you think his urinary output was originally satisfactory?

DR. KIPNIS: I would like to suggest the follow-

ing mechanism: Before his admission here, the patient probably experienced episodes of prolonged shock with resultant damage to his kidneys. However, urine flow was maintained because of an osmotic diuresis reflecting the markedly elevated blood sugar level. When his blood sugar level dropped, the osmotic load decreased and oliguria, reflecting the tubular damage sustained during shock, appeared.

DR. LILLIAN RECANT: I wondered about the possibility that hypokalemic alkalosis might be superimposed on his diabetic status; that would tend to increase his urinary output.

Dr. Kipnis: This patient, I believe, had marked depletion of his total body potassium stores. The suggestion that as a consequence he had hypokalemic nephropathy which added to the functional abnormalities caused by shock is an excellent one.

DR. MOORE: Dr. Morrin is familiar with the autopsy results, but I will ask him to try to remember his reactions as he saw the patient when he was alive. I suspect you think the most likely diagnosis is acute tubular necrosis, but forget that possibility for a moment. Tell me why you think the renal lesion could not be hypokalemic nephropathy.

DR. Peter A. F. Morrin: Hypokalemic nephropathy is not characterized by oliguria. Such patients may have some fall in filtration rate, but they do not have anuria and are characteristically polyuric. Some patients with diabetic acidosis who have come to autopsy have had changes in the tubules consistent with hypokalemia, but there is no evidence that hypokalemia could account for the oliguria in this patient.

DR. MOORE: Another diagnosis seriously considered at first by everyone was bilateral renal vein thrombosis, particularly since the degree of proteinuria was originally so great.

DR. MORRIN: I think that is a good possibility, Dr. Moore. Renal vein thrombosis can produce acute oliguria in association with dehydration. It is not uncommon in infants in whom it usually occurs in association with a septic course and ends fatally. This type of picture is less often seen in adults, and in the older age group the diagnosis may be difficult. The subsequent course in this patient with increasing urine output excludes complete bilateral infarction of the kidneys, and unilateral infarction would not explain the degree of azotemia. In addition, the retrograde pyelogram did not give us any

clue to bilateral renal vein thrombosis. However, in the initial stages we could not rule out

this diagnosis.

DR. MOORE: Still another diagnosis seriously considered was papillary necrosis. The house officers strained all his urine looking for bits of renal papillae that might pass. Can we eliminate this possibility, particularly in a person with severe diabetes?

DR. MORRIN: No, we certainly cannot. It was one of the diagnoses we favored quite strongly at first. This man had had an indwelling catheter for a couple of days if not longer. He had high fever and although we did not grow bacteria from his urine, he undoubtedly had received antibiotics in the outside hospital. In addition, the hematuria and the oliguria could be explained by papillary necrosis.

DR. Moore: A number of people recognized red blood cell casts in the urine; they wanted to be absolutely sure that nobody ever questioned their identity so they showed some of them to you. Red blood cell casts ordinarily mean

glomerulitis.

DR. MORRIN: We characteristically think of red blood cell casts as indicating glomerulitis, and we wondered if this patient could possibly have had an acute glomerulonephritis. That really seemed to be too coincidental and we found it very hard to believe. However, the possibility of some hypersensitivity state with an associated glomerulitis could not be excluded. I should point out, however, that I have on several occasions seen red blood cell casts in acute tubular necrosis.

DR. Moore: The diagnosis of acute tubular necrosis was attractive to many people. There were, however, three disturbing observations: (1) the high ratio of urinary to plasma creatinine, (2) the relatively low serum sodium, and (3) the fact that your laboratory found the osmolality of the urine to be higher than that of the plasma. Why did these three findings cast doubt on the diagnosis of acute tubular necrosis?

DR. MORRIN: It is generally believed, although by no means universally held, that the tubules in acute tubular necrosis almost completely lose their ability to function. The presence of a low sodium concentration in the urine indicates that the kidney tubules were still reabsorbing sodium. The presence of a urine more concentrated than the plasma likewise indicates that water reabsorption was occurring and concentration taking place. This means that

significant tubular function was present. Evidence of tubular function has been reported in occasional cases of acute tubular necrosis in which the diagnosis has been definitely established, and I have personally seen several such cases. But in the majority of instances the urine is isotonic and the urine sodium concentration tends to be significantly greater than 30 mEq. per L. With regard to the creatinine urine: plasma ratio, I can perhaps best explain this in the following way: The concentration of creatinine in the glomerular filtrate will be essentially the same as in the plasma. If one assumes that creatinine is neither secreted nor reabsorbed in its passage along the nephron, then the quantity of creatinine excreted in the urine will equal the quantity filtered during any given time interval. Water, however, will be reabsorbed along the length of the nephron, and so the concentration of creatinine in the urine will rise. The presence of a high creatinine urine: plasma ratio is therefore another indication that water reabsorption and hence tubular function is present. Approximately seven-eighths of the filtered water is reabsorbed in the proximal tubules. Normally, of course, fluid reabsorption continues in the distal tubule, so that only 1 to 2 per cent of the filtered water is excreted; the creatinine urine: plasma ratio may be over 100 in a normal subject. The creatinine urine: plasma ratio in acute tubular necrosis was studied by Bull and his co-workers * who did not find a value above 10 in any of six cases. We have studied more cases than that here, and have found a value above 10 in at least three; consequently, I do not think that this ratio is more than indicative of acute tubular necrosis.

DR. Moore: Now may I ask you to commit yourself? You said that acute glomerulonephritis was a possible diagnosis, although you thought that the coincidence would be at least remarkable; that bilateral renal vein thrombosis seems unlikely because of the subsequent course; that acute papillary necrosis remains a possible diagnosis; and that acute tubular necrosis is also a possible diagnosis, although you have cited several reasons for thinking that the diagnosis needs to be questioned. Do you have any additional diagnoses to make, or will you select one of these as the most probable?

DR. MORRIN: I think we have covered the

^{*} Bull, G. M., Joekes, A. M. and Lowe, K. G. Renal function studies in acute tubular necrosis. *Clin. Sc.*, 9: 379, 1950.

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differential diagnosis fairly thoroughly. I would suspect from the information and course of the patient after eleven days in the hospital, where urine output was increasing and blood urea nitrogen was beginning to fall, that acute tubular necrosis would fit the diagnosis most accurately. The fact that we had evidence of tubular function might indicate that it was a fairly mild acute tubular necrosis, and we may see minimal lesions at autopsy. In addition, there may be some evidence of a hypokalemic lesion in the kidneys.

DR. MOORE: Dr. King, everyone was constantly worried about the possibility of an infection. Many blood cultures were obtained, all of which were sterile. The house officers were worried about (1) the possibility of an infection in the urinary tract; (2) the nature of the pulmonary lesion; (3) the possibility of a peritoneal infection, possibly from rupture of a peptic ulcer, and (4) terminally, the possibility of a meningeal infection. Monilia were found in the urine on several occasions. Do you think that infection played a serious role in this man's illness? If the answer is "yes," where would you place the infection?

DR. M. KENTON KING: The answer to the question, Dr. Moore, is "no." We do not have any good evidence that an infectious disease played a major part in this patient's illness.

DR. MOORE: Dr. Brittingham, Dr. McAlister made quite a point of the fact that the lymph nodes in the hilar regions seemed to be enlarged. Does this information suggest anything specific to you?

DR. THOMAS E. BRITTINGHAM: No.

DR. Moore: You would just think that he had a pneumonitis from causes unknown and let it go at that?

DR. Brittingham: Patients with acute hemorrhagic pancreatitis commonly have densities in their chests.

DR. MOORE: You mean by that to imply that you think he really did have acute pancreatitis?

DR. BRITTINGHAM: Yes, as the underlying cause for his abdominal pain, diabetes and acute renal failure.

Dr. Moore: Acute hemorrhagic pancreatitis?

DR. BRITTINGHAM: Yes.

Dr. Shatz: The renal picture is compatible with what one frequently sees with acute hemorrhagic pancreatitis, as a result of marked loss in circulating blood volume. This would explain why the specific gravity in the urine was as

high as it was, as well as the other evidence of tubular function. I wonder how the renal group that cared for this patient ruled out the possibility of hypovolemia in the early stages of this patient's problem when there was evidence of shock and the possibility of hemorrhagic pancreatitis was present. The only efforts made to raise his blood pressure, as I can gather from the protocol, was by means of vasopressor drugs, rather than blood, plasma or plasma expanders.

DR. MOORE: Dr. Shatz, that is an error in the protocol, again because of brevity. It was suspected on a number of occasions that the patient might have been dehydrated. He was given at various times, once on Dr. Morrin's specific recommendation, as much as 1,000 or 2,000 additional cc. of fluid intravenously to try to compensate for any possible hypovolemia. The clinicians were riding on thin ice, not wanting to produce pulmonary overload, but still wanting

to correct the hypovolemia.

DR. SHATZ: The only effective way one can rectify the decreased circulating blood volume in hemorrhagic pancreatitis is by giving blood, plasma, albumin or plasma expanders. The situation in acute hemorrhagic pancreatitis has been likened to an "internal burn" because of the marked transudation of plasma into the peripancreatic area as well as into the peritoneal cavity. The fact that the administration of glucose or any other aqueous solutions did not correct the situation might not rule out the presence of hypovolemia. The current concept in the treatment of hemorrhagic pancreatitis is that serum, albumin and plasma are probably the two most important substances one can give to keep the patient alive. Another event that would be in keeping with hemorrhagic pancreatitis is the fact that the patient did so poorly on the artificial kidney, because about a week or so after the initial episode, internal hemorrhage may result from the digestion of blood vessels by the pancreatic enzymes. This patient was placed on the artificial kidney and given large doses of heparin. Could this have precipitated an intraperitoneal hemorrhage and the shock which occurred during this procedure? I think that the possibility of hemorrhagic pancreatitis is a good one here, despite some objections. I do not see any other better explanation, and I would agree with Dr. Brittingham.

Dr. Moore: The renal team decided initially to use peritoneal dialysis because they did not

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want to use heparin. But after the series of convulsions had changed the picture, and he had been given so much barbiturate and was comatose again, they thought it necessary to change to hemodialysis.

Dr. Berg, what do you think about the nature of the intracranial lesion? Remember, this man had headache and seizures, possibly beginning in the right hand, then dilatation of his pupils during the dialysis; he was found to have red

blood cells in his spinal fluid.

DR. LEONARD BERG: Red blood cells and xanthochromia. This certainly sounds like the development of an acute intracranial hemorrhage, most likely into the substance of the brain; that is why there was not more blood visible in the spinal fluid. The hemorrhage could have been in either cerebral hemisphere. The early dilatation of the right pupil would suggest it was right hemisphere, but your note about the right arm having focal convulsions would suggest it is the left. Of course, it could be both. There is a remote possibility that this was simply the development of acute generalized cerebral edema, but it certainly sounds much more like a bleeding episode. Now, the problem is why he should be bleeding at that time. Massive intracranial bleeding is unusual in uremia, unless there is associated hypertension. As you pointed out, this occurred before he had dialysis, so heparin should not be responsible. It would raise the question in my mind whether there was another disease of blood vessels in the brain that led to the hemorrhage: an aneurysm or angiitis. I think that he had intracerebral hemorrhage, right or left or both, and I would be quite concerned that there was underlying disease of blood vessels in the brain.

DR. MOORE: Dr. Reichlin, should serious consideration be given to a lesion, perhaps a neoplastic lesion, in the central nervous system, involving perhaps the floor of the third ventricle, which was responsible for precipitating diabetes and for the initial spinal fluid pressure of 360 mm. water?

DR. SEYMOUR REICHLIN: That possibility is very unlikely. Among other reasons, this man's carbohydrate metabolic disturbance was typical of diabetes mellitus rather than of cerebral hyperglycemia. Since this is a clinicopathologic conference, I had considered an unusual cause of shock, coma and death with evidence of intracranial bleeding, namely, hemorrhage into the pituitary. This is a well known complication of

pituitary tumors,* and has also been observed in diabetes. A number of findings, however, may be cited against this diagnosis. The spinal fluid pressure in that condition is usually high, local pressure symptoms are manifest and as far as I know convulsions do not occur. The clinical findings resemble subarachnoid hemorrhage.

Dr. Moore: Dr. Reiss, I am aware that you know what the gross pathologic findings were, but you took care of this man during the last few days of his life. Do you care to comment about

any phase of his illness?

DR. ERIC REISS: I saw this patient during a very limited portion of his hospital stay and, happily, at a time when he was doing well. The practical point that troubled us most was the abdomen. I would like to emphasize again that it was soft, and that normal peristaltic activity was audible. At that time, the patient was completely oriented and cooperative. In answer to Dr. Shatz, at this particular late stage I thought that we had strong evidence for tubular necrosis or some other organic renal impairment. The vital signs then were normal, and there were no clinical signs of extracellular fluid depletion. Most important, the urine sodium was high. In simple extracellular fluid deficiency the urinary sodium concentration would be very low.

Dr. Daughaday: We are really up against it if we try to explain the entire course on the basis of diabetes; I am not willing to do that. Actually we really have no unequivocal evidence that this man was ever in severe diabetic acidosis. When he came to us he was in moderate ketosis, but not acidosis; I am attracted by Dr. Shatz's

concept of pancreatitis.

DR. GIESELMAN: I was interested in the roentgenographic presentation and would like to ask the radiologist if the contour of the right diaphragm disturbed him at all. It seemed to me that on the first picture the diaphragms were fairly normal in their relative heights and normally curved; the second one had a rather prominent hump in the middle of the right diaphragm; and on the last roentgenogram the right leaf of the diaphragm was more elevated than the left. Should we consider infradiaphragmatic disease—some sort of suppurative process?

DR. McALISTER: The hump noted on the right in the second chest roentgenogram represented subpulmonary fluid. The changes on the

^{*} UIHLEIN, A., BALFOUR, W. M. and DONOVAN, P. F. Acute hemorrhage into pituitary adenomas. *J. Neurosurg.*, 14: 140, 1957.

third and last chest roentgenogram shown were the result of positioning plus subpulmonary fluid.

DR. MORRIN: We get a rather misleading picture from the protocol in regard to the terminal course. This man had respiratory difficulty before he was placed on the artificial kidney. It did not develop suddenly during dialysis, but slowly became worse, necessitating intubation. At this point we stopped dialysis and gave some protamine to correct the clotting time to normal. About this time we noted dilatation of the pupil. There was no sudden, dramatic deterioration in respiratory function. The only other comment I would like to make is to clarify our reason for performing dialysis in this patient. Convulsions and coma probably occur in about 30 per cent of patients with acute renal failure. without demonstrable central nervous system disease, and can frequently be alleviated by dialysis. We believed there was a strong indication for immediate dialysis in this case. We might have preferred to perform a peritoneal dialysis, but due to the urgency and the possibility of pancreatitis, hemodialysis was employed.

DR. Moore: I would think that the pathologist might show us some evidence of pancreatitis, but would be surprised if he showed us the changes of acute hemorrhagic pancreatitis. The patient, of course, had diabetes. The renal lesions might be a combination of hypokalemic nephropathy and of acute tubular necrosis. There should be some evidence of pneumonitis which did not play too important a role in his illness. I suspect that he had a terminal intracranial hemorrhage, but do not know why. The suggestion has been made by several people that angiitis or polyarteritis might be present; this is an interesting suggestion, but personally I do not believe there are enough supporting data.

PATHOLOGIC DISCUSSION

DR. GEORGE SORENSON: The patient's primary disease was diabetes mellitus. This apparently developed spontaneously; he did not have pancreatitis. The pancreatic islets demonstrated marked degranulation of beta cells and granules could be identified in only a few of these cells. (Fig. 1.) The number of islets appeared to be normal. As you recall, in patients with juvenile diabetes the number of islets is commonly decreased; while in diabetes developing at maturity, they are normal in number.

The final course of this patient was apparently

initiated about ten or eleven days prior to his death during the episodes of severe hypotension. The effect of this was reflected in the gross appearance of the kidneys at the time of autopsy. The kidneys each weighed approximately 220 gm. They were grossly swollen and the cut surfaces bulged. The cortical regions were pale and stood out in marked contrast to the medullary regions. (Fig. 2.) There were also some recent hemorrhages in the pelvis of each kidney. Microscopic study revealed the typical findings of acute tubular necrosis. (Fig. 3 and 4.) The lower nephrons contained frequent eosinophilic casts and associated with the casts was marked degeneration of the tubular epithelium. Also present was interstitial edema and a moderate interstitial infiltrate of inflammatory cells which included lymphocytes, a few plasma cells, some eosinophils and a few neutrophils. The tubular necrosis was focal but quite distinct and involved some of the proximal as well as the distal tubules. There were several small infarcts in the kidneys. These were probably due to emboli, although a source of emboli was not found.

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This man's renal failure had a particularly damaging effect upon the central nervous system; this damage eventually required that he be placed in a respirator. At autopsy the brain was severely swollen; it weighed 1,350 gm. There was extreme, bilateral uncal grooving and marked herniation of the cerebellar tonsils. Microscopically, severe edema and widespread, hypoxic degenerative changes were evident in the neurons. The latter was well demonstrated in the cerebellum where many of the Purkinje cells demonstrated homogenizing degeneration. The cytoplasm of these injured cells were eosinophilic and the nuclei were shrunken and less basophilic than normally. Similar changes were found in some of the cortical neurons.

There was also a rather recent, small infarct involving about one third of the pituitary. This probably occurred terminally and, if this had any effect at all, it may have lessened the severity of his diabetes. There was a recent thrombus in the left transverse and sigmoid dural sinuses without morphologic effect on the brain. There was no cerebral hemorrhage. A possible explanation for the neurologic signs is that they were due to the uremia and the cerebral edema.

The patient also had a rather severe tracheal bronchitis, which probably developed late in his course, and an acute bronchopneumonia. There were 500 cc. of pleural effusion on each side and

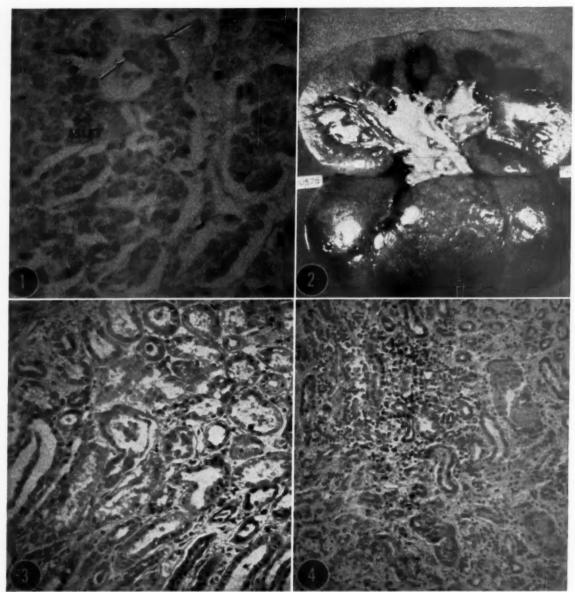


Fig. 1. Photomicrograph illustrating a portion of a pancreatic islet on the left and some pancreatic acinar tissue on the right. Beta cells reveal severe degranulation except for an occasional cell (arrows). Aldehyde fusion—

- Fig. 2. The kidneys were pale, swollen and the corticomedullary junctions were sharply demarcated.
- Fig. 3. Portion of renal medulla with necrosis of the tubular epithelium. Hematoxylin and eosin stain.
- Fig. 4. Another photomicrograph of renal medullas in which there is tubular epithelial necrosis, cast formation and moderate inflammatory infiltrate. Hematoxylin and eosin stain.

250 cc. of acitic fluid. The enlargement of the hilar lymph nodes was caused by remote granulomatous disease, probably tuberculosis.

In summary then, this was a patient with diabetes in whom hypotension, acute tubular necrosis and renal failure developed. He died mainly because of the disastrous effects of the renal failure on the central nervous system.

Final anatomic diagnoses were marked degranulation of the beta cells of the pancreas consistent with diabetes mellitus; acute tubular necrosis; cerebral edema, marked with uncal grooving and herniation of cerebellar tonsils; homogenizing degeneration of neurons in brain consistent with hypoxic damage; recent small infarct of pituitary; acute tracheobronchitis and

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bronchopneumonia; bilateral pleural effusions, 500 cc. each; ascites 250 cc.; fibrocaseous granulomatous nodules in tracheal and tracheal-bronchial lymph nodes.

DISCUSSION

DR. MOORE: You saw no lesion in the stomach or elsewhere in the gastrointestinal tract which might have explained his pain?

Dr. Sorenson: No. There was rather severe edema throughout the gastrointestinal tract, along with some congestion and scattered petechiae. Two small superficial ulcers were found in the jejunum, but I think all these changes developed terminally.

DR. MOORE: When you do find changes of hypokalemic nephropathy, what do you see?

DR. MORRIN: The usual picture is vacuolization mainly in the proximal tubules and to a lesser extent in the distal tubules. Lesions in the collecting duct are more common in the experimental animal. Dr. Daughaday pointed out that if this man had glycogen in his tubules, it might be very hard to make the diagnosis of vacuolization in the microsections, unless the sections were specifically stained for glycogen.

Dr. Brittingham: Hyperpyrexia may have been responsible for this man's brain and kidney disease. He came into the hospital with a temperature of almost 107°F. and once the body temperature reaches 106° or more both acute tubular necrosis and generalized brain damage are very common. That such a temperature developed is not surprising, because he arrived at the Barnes Hospital in a state of extreme dehydration, with serum hyperosmolarity equivalent to a serum sodium of about 167 mEq. per L. (as a result of his high blood glucose level, together with the serum sodium level of 155 mEq. per L.). Hypertonicity would have set him up to decrease his sweating and develop a hyperpyrexic reaction from whatever was giving him fever. I emphasize the hyperpyrexia, because I had been unaware of uncomplicated diabetic acidosis alone causing severe acute tubular necrosis in the kidneys.

DR. BERG: Was the sinus thrombosis situated in such a location as to contribute to cerebral edema? The course seems peculiar for hyperpyrexia in that the patient awoke a few hours after coming into the hospital and was quite alert for ten days or so before suddenly going into

DR. Moore: Dr. Daughaday, the ordinary vol. 31, NOVEMBER 1961

reaction in the central nervous system when diabetic coma and a high blood sugar level are present is dehydration; we had evidence to indicate that this patient's serum sodium level was high to go along with dehydration. Yet his initial spinal fluid pressure was 360 mm. water. How do you fit all that together?

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DR. DAUGHADAY: I am bothered by this whole initial episode. I do not know many people who have reported measuring cerebral spinal fluid pressure in diabetic acidosis so I cannot definitely say that it should be low, but this is what I would expect.

DR. MICHAEL M. KARL: We are still lacking an explanation for the hypotension.

DR. KIPNIS: One of the major complications appearing late in the course of diabetic acidosis is vascular collapse. The possibility that this may reflect severe potassium depletion or adrenocortical insufficiency is intriguing especially in view of the gratifying response to intravenous hydrocortisone therapy and potassium repletion.

DR. DAUGHADAY: I would agree that hypokalemia is a most important factor contributing to late vascular collapse in our diabetic acidosis group here.

DR. REICHLIN: We do not have a good history about the promazine and the Demerol® that this man received at the very beginning of his illness. Patients with metabolic disturbances of the brain due to anoxia, anemia, diabetic acidosis, myxedema and the like, are extremely susceptible to narcotic and tranquilizing drugs. A fair-sized dose of a promazine drug in a patient who was vulnerable for other reasons could produce shock and coma.

DR. Sol Sherry: What disturbs me relative to the previous discussion is the almost exclusive emphasis on potassium depletion. It is fashionable and reasonable to consider a hypokalemic nephropathy, but in this particular patient the large amounts of insulin and carbohydrate used in his treatment could have induced a rather precipitous fall in the serum potassium level, sufficient to explain the paralysis which developed, but insufficient to produce the chronic effects of potassium depletion. Furthermore, we often lose sight of the fact that in patients who have persistent vomiting over a period of a week or so considerable amount of alkalosis and dehydration may develop which may contribute to renal failure directly in addition to the effects of potassium loss. To explain everything on the

bases of hypokalemia, without considering that other associated fluid electrolyte and acid base difficulties may contribute to the nephropathy, is, in my opinion, laying too much stress on one factor.

DR. REISS: Dr. Sherry's point is very well taken. On the other hand, we do have good evidence of a severe potassium depletion in this man; he received massive amounts of potassium and his serum potassium stayed low. This can-

not occur, as far as I know, except under a condition of great depletion. Is that not correct?

DR. SHERRY: The patient did receive Lente insulin in large amounts; its effects could have been maintained for a considerable period of time. The available data seem insufficient to resolve the question as to how much of his hypokalemia was due to actual depletion of body potassium, and how much was iatrogenically induced.

Fanconi Syndrome with Hypouricemia in an Adult*

Family Study

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THE Fanconi syndrome is rare in adults. Eighteen cases in adults reported up to 1957 were collected by Wallis and Engle [1], and at least seven more have since been recorded [2-8]. In only two of these cases was an hereditary basis established for this metabolic disorder [9,10]. In the case described herein nine other members of the family were found to be affected in some way.

CASE REPORT

The patient (G. H.), a twenty-eight year old Tunisian born married woman, had enjoyed good health until 1957 when, shortly after her fourth delivery, she began to complain of diffuse bone pain. In 1958 roent-genologic examination in another hospital revealed multiple pseudofractures in the right femur, right humerus, both fibulas and ribs. Laboratory data supplied by this hospital are summarized in Table I (column 1). Osteomalacia was diagnosed and the patient was treated with large doses of vitamin D, calcium gluconate and a mixture of citric acid salts. Her condition improved and after discharge the same treatment was continued.

In July 1959 she was referred to our department for further investigation. At that time, she was free of complaints.

The patient was a thin woman of small stature, 143 cm. in height and 42 kg. in weight. She had a waddling gait and a severe kyphoscoliosis. The liver and spleen were palpable 3 and 6 cm., respectively, below the costal margin. Physical examination showed no other abnormalities. Funduscopic and slit lamp examination of the eyes were within normal limits. No findings suggestive of Wilson's disease were noted.

The results of the routine laboratory investigation are presented in Table 1 (column 2). On paper electrophoresis of the serum proteins, albumin comprised 38.1 per cent, alpha₁ globulin 5 per cent, alpha₂ globulin 10.5 per cent, beta globulin 14.2 per cent, and gamma globulin 32.2 per cent. The serum level of amino acids was 6 to 7 mg. per cent. The results of the bromsulphalein test showed 5 per cent retention. The pH of the urine on a mixed diet was 6.5 to 7.5.

TABLE I
ROUTINE LABORATORY DATA

Data	1958	1959
Hemoglobin (gm. %)	13.0	15.3
Erythrocyte sedimentation rate	16/	5/
(Westergren), (mm./hr.)	16/36	5/10
Serum (or plasma)	8.7-9.9	10.2-12.4
Calcium (mg. %)	2.9-3.8	1.7-3.0
Inorganic phosphorus (mg. %). Alkaline phosphatase, Bodan-	2.9-3.6	1.7-3.0
sky units	10 1-17 7	10-17.2
Sodium (mEq./L.)	144.0	136.0
Potassium (mEq./L.)	4.0	4.0
Chloride (mEq./L.)	104.0	96.0
Bicarbonate (mEq./L.)		21-25
Urea (mg. %)	25.0	26.0
Uric acid (mg. %)	2.4	0.8-2.2
Creatinine (mg. %)	0.96	0.98
Albumin (gm. %)	4.5	4.0
Globulin (gm. %)	2.0	3.5-3.8
Cephalin flocculation		+++
Thymol turbidity (units)	5-6	4
Thymol flocculation	++	+++
Cholesterol (mg. %)	82.0	218.0

^{*} From the Department of Medicine A, Rothschild Hadassah University Hospital, and the Laboratory of Clinical Research, Hebrew University—Hadassah Medical School, Jerusalem, Israel. This study was supported by a grant from the Teva Middle East Pharmaceutical and Chemical Works, Ltd., Jerusalem, Israel. Manuscript received September 1, 1960.



Fig. 1. Roentgenogram of thoracic spine and ribs. Severe scoliosis, broad Looser zones of the eighth, to eleventh left ribs (indicated by arrows).

Proteinuria up to 1.5 gm. per L. was constantly present. No Bence Jones protein was found. Urinary excretion of alpha-amino nitrogen ranged from 420 to 800 mg. per twenty-four hours. Paper chromatography of the urine revealed large amounts of arginine, aspartic acid, glutamic acid, glycine, histidine, leucine, methionine, phenylalanine, proline, serine, threonine, tyrosine, valine and unidentified sulfhydrylcontaining amino acids. Following meals, a reducing substance identified by paper chromatography as glucose was repeatedly found in the urine.

The sternal bone marrow was normal. A renal biopsy specimen revealed normal kidney tissue with small areas of fibrosis.

Roentgenologic examination (Dr. M. Fraenkel) of the entire skeleton showed multiple healed fractures of the left eighth, ninth, tenth and eleventh ribs, and clearly visible fracture lines without callus formation were seen in the right tenth rib. (Fig. 1.) On the proximal posterior face of the right humerus and on the proximal medial part of the right femoral shaft there were infractions in various stages of healing. Healed fractures were seen in the upper third of both fibulas. (Fig. 2.) Intravenous pyelography did not reveal any calcified shadows, and there was good excretion from both kidneys, which were of normal size.



Fig. 2. Roentgenograms of tibias and fibulas. Old fractures with callus formation in the upper third of both fibulas.

SPECIAL INVESTIGATIONS

Inulin and Endogenous Creatinine Clearance.* Renal clearance studies showed a moderately reduced glomerular filtration. (Table II.) The average inulin clearance was 78 ml. per minute. The twenty-four endogenous creatinine clearance ranged from 44 to 78 ml. per minute.

Inorganic Phosphate Clearance. Simultaneous determination of inorganic phosphate and inulin clearances revealed an average phosphate clearance of 24.2 ml. per minute, with a C_P: C_{inulin} ratio of 0.33. The twenty-four-hour clearance studies of phosphate and creatinine showed a similar ratio. This is considerably above normal values at serum phosphate concentrations between 2 and 4 mg. per cent, and reflects a defect in the tubular reabsorption of phosphate.

Uric Acid Clearance. The average clearance of urate as determined during the course of inulin clearance was 91 ml. per minute, corresponding to a Curate: Cinulin ratio of 1.16. Subsequent determinations of the twenty-four-hour clearance of uric acid and endogenous creatinine showed the urate clearance to be 55 to 65 ml. per minute with a Curate: Cr ratio of 0.71 to 0.86. The abnormally high values indicate reduced tubular urate reabsorption and/or increased excretion of uric acid by the tubules. The administration of 2 gm. per day of probenecid had no significant effect upon the urate clearance.

* All clearance values in the text and in Table II are corrected to 1.73 square meter body surface area.

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TABLE II
RENAL CLEARANCE STUDIES ON PROPOSITUS

	Urine	Inulin or	Urio	Acid	Phos	sphate	Cua:Cin	C _P :C _{IN}
Date	Flow (ml./min.)	Creatinine Clearance (ml./min.)	Serum (mg. %)	Clearance (ml./min.)	Serum Clearance (mg. %) (ml./min.)		or Cua:Ccr	or C _P :C _{CR}
			Sh	ort Term Experi	iments			
Nov. 8	1.0 1.1 0.91	82 82 71	0.83 0.79 0.90	100 100 73	1.81 1.84 1.73	25.1 24.8 22.8	1.22 1.22 1.03	0.34 0.34 0.32
Average		78	Twent	91 y-Four Hour Ex	periments	24.2	1.16	0.33
Aug. 31	1.25	78	0.88	55			0.71	
Sept. 1	1.67	74	0.98	65			0.86	
July 26	0.77	55			2.74	16.6		0.31
July 28	1.08	53			2.14	13.7		0.25
July 29	0.77	44			2.58	18.2		0.42
Average		50				16.2		

Glucose Tolerance Test. During a glucose tolerance test the blood glucose curve was normal, but glycosuria was present throughout, being maximal during the third half-hour period. (Fig. 3.) Glucose excretion during the second half-hour period was 18 mg. per minute, the average glucose plasma level being 127 mg. per cent. The filtered load, as calculated from the previously established inulin values, was 99 mg. per minute. Thus only 82 per cent of the glucose filtered load was reabsorbed, as contrasted with complete reabsorption at normal glucose plasma levels.

Response to Intravenous Calcium Load. It was shown by Schilling and Laszlo [11] that patients with osteomalacia, when given a load of calcium intravenously, excrete less calcium in the urine than do normal patients. A calcium infusion test was therefore performed, using the method described by Nordin and Fraser [12]. Calcium gluconate was given intravenously over a fourhour period in a dose of 15 mg. calcium per kg. body weight. The serum calcium value rose from 10.8 mg. per cent to 12.4 mg. per cent and returned to the initial value four hours later. The net urinary excretion of calcium during the twelve-hour period after starting the infusion was 18 per cent of the administered dose, which is within the range of 2 to 27 per cent usually

found in patients suffering from osteomalacia [12].

Response to Ammonium Chloride Load. The patient's urine was constantly alkaline on routine examinations, as is usual in patients with the Fanconi syndrome. However, the administration of 0.1 gm. per kg. body weight of ammonium chloride caused the urinary pH to fall from 7.3 to 5 within four hours. From two to eight hours following ingestion of ammonium chloride the mean excretion of ammonia was 50 µEq. per

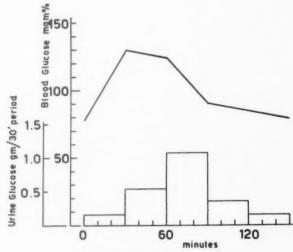


Fig. 3. Glucose tolerance test.

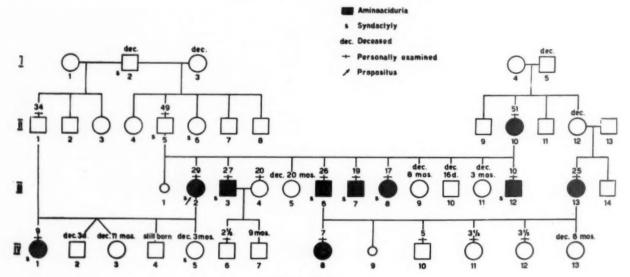


Fig. 4. Pedigree.

minute, and that of titratable acid was 35 μ Eq. per minute. These values are within the range found normal by Wrong and Davies [13].

Response to Pitressin. In some cases of the Fanconi syndrome a defect in tubular reabsorption of water in the presence of ADH has been reported. Since our patient showed mild polyuria, her response to the administration of exogenous pitressin was examined. During glucose infusion and after the urinary flow had become stable at about 5 ml. per minute, intravenous injection of either 15 or 30 milliunits of pitressin reduced the urine output by only about 40 per cent. Osmolarity rose from 146 to 220 mOsm., and from 186 to 236 mOsm., respectively. This poor response, indicating diminished sensitivity to pitressin, may have been due to a primary tubular defect in the handling of water, or connected with the alkalinity of the urine, or with the presence of other abnormalities affecting its ionic composition [15].

FAMILY STUDIES

The pedigree of the patient is shown in Figure 4. Her parents denied consanguinity.

The patient is the eldest of six living children. Four others died in infancy of unknown cause. She married her father's half brother (II₁), and has a nine year old mentally retarded daughter suffering from congenital ptosis (IV₁). Three other children, including non-identical twins, died during their first year of life. A fourth was stillborn.

Fifteen members of the patient's family were personally examined. They were all of normal

appearance except for a nineteen year old brother (III₇), who was frail and underweight. This brother suffered from night blindness due to retinitis pigmentosa, and had hypoplasia of the upper lobe of the right lung. In a seventeen year old sister, (III₈), polyuria and polydypsia developed at the age of thirteen years, and her urine contained sugar. These symptoms have since subsided. No skeletal deformities were detected in the other members of the family. The only physical abnormality was the occurrence of syndactyly of the second and third toes in eight persons, including the patient. This anomaly

TABLE III
URINE FINDINGS OF THE PATIENT AND HER FAMILY

Subjects	Kinship	Age (yr.)	Amino- aciduria*	Glyco- suria	Albumi nuria
I ₁ ,A. H.	Grandmother	73	N		
4,Z. M.	Grandmother	78	N		
II1,M. H.	Half uncle	34	N		
2,N. H.	Half uncle	47	N		
3,S. H.	Half aunt	45	N		
5,M. H.	Father	49	N		
8,I. H.	Uncle	55	N	***	
9,H. M.	Uncle	53	N		
10,H. H.	Mother	51	+		
III2,G. H.	Propositus	29	+	+	+
3,M. H.	Brother	27	+	+	+
6,A. H.	Brother	26	+		* *
7,H. H.	Brother	19	+ !	+	+
s,R. H.	Sister	17	+	+	+
12,A. H.	Brother	10	+		
13,L. H.	Cousin	25	+ +	* * *	***
IV ₁ ,M. H.	Daughter	9	+	* * *	
6,S. H.	Nephew	21/2	N		
s,M. H.	Niece	7	+		
10,A. H.	Nephew	5	N		
11,Y. H.	Niece	31/2	N	***	***
12,J. H.	Niece	21/2	N	* * *	

^{*}N = normal.

Table IV
CHROMATOGRAPHIC FINDINGS IN FAMILY MEMBERS
WITH AMINOACIDURIA

Subjects	Alanine	Arginine	Aspartic Acid	Cystine	Glutamic Acid	Glycine	Histidine	Hydroxyproline	Leucine	Lysine	Methionine	Phenylalanine	Proline	Serine	Threonine	Tyrosine	Valine	SH Groups
II10,H. H.			+		+	+	+	+						+		+		+
III2,G. H.	1	+	+		+	+	+		+		+	+	+	+	+	+	+	+
3,M. H.	+	+	+		+	+	+	+						+	+	+	+	
6,A. H.		+	+		+				* *	+					+	+	+	
7,H. H.		+	+		+	+	+		+			+			+	+	+	
s,R. H.		+	+		+	+	+	+						+	+	+	+	
12,A. H.	+		+		+	+			+			+		+	+	+	+	
12,L. H.		+	+		+	+	+							+	+	+		
IV ₁ ,M. H.	+	+			+	+	+		+	+		+	+	+	+		+	+
8, M. H.		+	+		+	+	+	+						+	+	+		+

had apparently also been present in three other relatives, now deceased.

Samples of urine from twenty-one relatives were examined. The findings are summarized in Table III. Mild albuminuria and glycosuria were found in two brothers and the sister. Aminoaciduria was found in nine members.* The findings of the chromatographic studies are summarized in Table IV.

The blood of seven relatives was examined. The serum phosphate and alkaline phosphatase levels were normal. Low serum uric acid values

were found in five subjects. Subsequently, short term clearance studies of creatinine and uric acid were carried out, the urine being collected during a four-hour period in the non-fasting state. The subjects were at home, following their usual routines, but were encouraged to drink liberally to ensure a copious flow of urine. Blood was drawn about half way through the period. For comparison, a similar test was carried out on the patient. The results are summarized in Table v.* The blood uric acid values corresponded closely with those previously obtained. A high uric acid clearance was found in every instance. The highest figures (38 to 64 ml. per minute) were found in the patient and in three siblings who, like the patient, also presented the triad of massive aminoaciduria, albuminuria and glycosuria.

A decreased creatinine clearance (50 to 81 ml. per minute) was found in four subjects, in contrast to their elevated uric acid clearance. This was reflected in a very high urate: creatinine clearance ratio (0.34 to 1.2).

The sister (III₈) had an unusually high creatinine clearance of 214 ml. per minute. In consequence, she had a nearly normal C_{urate}: C_{Cr} ratio despite the high uric acid clearance value.

COMMENTS

The syndrome described by Fanconi in children [16] consists of dwarfism, rickets, albumi-

Table v
Four-hour clearance studies of the patient and some relatives*

Name			Uric	Acid	Crea		
	Kinship	Volume (ml./min.)	Serum (mg. %)	Clearance (ml./min.)	Serum (mg. %)	Clearance (ml./min.)	Clearance Ratio
М. Н.	Father	4.2	3.4-3.7†	22.4	0.77	143	0.15
H. H.	Mother	0.9	1.0-1.3†	19	0.57	118	0.16
G. H.	Propositus	1.4	0.9	64	0.77	53	1.2
M. H.	Brother	3.2	1.5	44	1.74	50	0.88
A. H.	Brother	2.1	3.8-4.2†	14	0.75	150	0.09
Н. Н.	Brother	1.7	1.3-2.1†	47	1.24	81	0.58
R. H.	Sister	4.1	1.2-1.5†	38	0.65	214	0.17
M. H.	Daughter	1.7	2.4	19	0.38	56	0.34

^{*} The clearance values are not calculated to 1.73 square meter body surface area.

^{*} Aminoaciduria was diagnosed if the normally occurring amino acids, glycine, glutamic acid, histidine and lysine were found in increased amount and other amino acids were also present.

 $^{^{}st}$ These clearance values are not corrected to 1.73 square meter area.

[†] Values determined on a previous occasion.

nuria, glycosuria and hypophosphatemia. It has been attributed to impaired ability of the proximal convoluted renal tubule to reabsorb glucose, phosphate, amino acids, bicarbonate, and occasionally potassium. Although this disorder is mostly encountered in children, it has also been reported, usually in less severe form, in

adults [1-8].

The case herein described fulfilled all the criteria of this syndrome, whilst some of the relatives of the patient showed various facets of the disturbance. Involvement of siblings has been reported in children [17,18], but rarely in adults. Stowers and Dent [19] reported glycosuria and bone deformities in five adult relatives of a patient. However, further investigations [10] revealed abnormal aminoaciduria of the lysine-arginine type in only one of twentyfour members, and this the authors considered a chance occurrence rather than proof of an hereditary anomaly. Only two well documented cases in adults, in whom the hereditary nature of the disease was definitely proved, have been reported. Linder et al. [9] described the disease in an adult Negro woman whose sixteen year old sister also suffered from spontaneous fractures, glycosuria, albuminuria and hypophosphatemia. The other siblings were unaffected. Dent and Harris [10] reported a case in a forty-one year old woman. Three adult siblings had aminoaciduria, glycosuria, mild acidosis and hypophosphatemia. They differed from their affected sister in their healthy appearance, and lack of clinical or roentgenologic signs of bone involvement. The authors considered the abnormal siblings to have a constitution genetically similar to that of the patient, and suggested that aminoaciduria, glycosuria and hypophosphatemia should be regarded as the essential features of the condition, and that although bone lesions may later develop these are not necessarily associated. In their view the renal abnormality was not present at birth in the case of the siblings, for otherwise more developmental and skeletal anomalies should have appeared. Our findings of aminoaciduria in three children below ten years of age support the view that an hereditary anomaly may be evident in early childhood. The involvement of ten members of one family through three generations seems to be an outstanding feature.

The renal abnormalities varied in the affected members, and ranged from the triad of aminoaciduria, glycosuria and albuminuria in four subjects, to aminoaciduria alone in six other relatives. Whereas the patient herself presented the complete Fanconi syndrome, including bone manifestations, the other members of the family only had biochemical abnormalities, possessing what might be termed a "Fanconi trait."

It is not clear why osteomalacia developed in only this patient. Her pregnancies, one resulting in twins and three followed by periods of lactation, may have been precipitating factors. In her cousin (III₁₃), however, who had had six pregnancies, osteomalacia has not so far developed. Differing degrees of tubular dysfunction, or of living and nutritional standards, may have been responsible for this difference.

In addition to the classic features of the Fanconi syndrome, the patient had a very low serum uric acid level and a much elevated uric acid clearance value. The occurrence of hypouricemia in the Fanconi syndrome does not seem to have been noted by most authors. Uric acid levels were examined in only six of eighteen adult patients reviewed by Wallis and Engle [1], and in none of the seven subsequently reported cases [2-8]. It was low in three instances, being from 1.4 to 1.7 mg. per cent. Detailed clearance studies were made in a case reported by Sirota and Hamerman [20]. The patient had a low plasma concentration, and a high uric acid clearance of 25.7 ml. per minute. In this case the high C_{urate}: C_{inulin} ratio of 98.5, and the lack of response to therapy with Benemid, were interpreted as evidence of complete failure of urate reabsorption by the renal tubules. A similar abnormal tubular handling of urate was found in our patient who also had a Curate: Cinulin ratio exceeding unity, suggesting active tubular excretion of urate [21].

Low serum uric acid levels and high urate clearance values were found in several close relatives of the patient, whilst in two instances the blood uric acid level was normal and the uric acid clearance moderately elevated. A search of the available literature has not revealed any other account of the familial occurrence of disturbed urate excretion in association with the Fanconi syndrome. The findings suggest that abnormal handling of the urate by the renal tubules may be more frequent in the Fanconi syndrome than has been realized.

The finding of retinitis pigmentosa, present in the patient's brother (III₇), was also reported in a few cases of the Fanconi syndrome by Linder et al. [9,14]. They suggested that the same genetic defect might cause renal tubular deficiencies and

retinal degeneration. Our findings are consistent with this hypothesis. The association of retinitis pigmentosa with other familial anomalies, such as the Laurence-Moon-Biedl syndrome, is well known.

Syndactyly, the only morphologic familial abnormality encountered in this family, was found in eight members and apparently had been present in three others. The "Fanconi trait" occurred on the maternal side of the patient's family, whereas syndactyly evidently came from the paternal side. The two conditions thus seem to occur independently in this family.

SUMMARY

A case of familial Fanconi syndrome in a twenty-eight year old woman is described. The patient had osteomalacia, aminoaciduria, glycosuria, phosphaturia, albuminuria, hypouricemia and mild polyuria.

Nine relatives were affected in various degrees. Abnormal aminoaciduria was found in every instance. The triad of aminoaciduria, glycosuria and albuminuria was present in two of the patient's brothers and in her sister. Low serum uric acid levels and elevated uric acid clearance values were found in the patient and in four members of her family.

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APPENDIX

The following analytic methods were used in the preceding investigation: Creatinine [22], uric acid [23], amino acids [24], inorganic phosphate [25], calcium (modification) [26]. Osmolarity was determined by a thermistor type freezing point apparatus. Two dimensional paper chromatography was performed, using phenol and butanol-water-acetic acid (4:4:1).

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Hemolytic Anemia of Necrotic Arachnidism*

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HEMOLYTIC anemia is an uncommon but serious complication of necrotic arachnidism. Fourteen well documented cases of this syndrome have been recorded [1–13], three in the American and eleven in the South American medical literature. It is our purpose to report two cases of acute hemolytic anemia resulting from the bite of unidentified insects; to suggest by a review of the pertinent literature that the etiologic agent is a spider of the family loxoscelidae; and to discuss possible mechanisms of the hemolysis.

CASE REPORTS

CASE I. A forty-four year old school bus driver was admitted to the Vanderbilt University Hospital on December 3, 1959, because of jaundice and anemia. Six days prior to admission, while pulling on his trousers, he noted a sharp pain on the left side of his scrotum. Although the patient was unable to find the offending insect he stated that there were many spiders in and near his home. No local lesion was noted at the time of the injury but the patient soon began to experience rather severe burning pain in the scrotum, with swelling and tenderness, followed by generalized aching pain, malaise, nausea, vomiting and fever. He was seen by a physician, given an injection of ACTH, and was admitted to a local hospital on the following morning. Hemoglobinuria was then noted and a hematocrit of 20 per cent was recorded. The patient was treated with antibiotics and steroids. On the third day following the bite a scarlatiniform rash appeared. The patient did poorly and on the morning of the sixth day he was transferred to the Vanderbilt University Hospital because of jaundice. The past and family histories were noncontributory. There was no history of previous insect bite, known allergy or blood dyscrasia.

The patient was an obese white man who was acutely ill. The temperature was 102.4°F., pulse 120, respirations 24 and blood pressure 170/80 mm. Hg. The skin was pale and jaundiced, and there was a generalized erythematous scarlatiniform rash which was most prominent on the trunk. The left side of the scrotum was covered with a dry, necrotic black

eschar. (Fig. 1.) The scleras were icteric. A sinus tachycardia was present, and there was a hemic murmur along the left sternal border. The liver and spleen were not palpable. The remainder of the examination was non-contributory except for marked prostration and labored breathing.

The result of the serologic test for syphilis was negative. The urine was very dark and gave a 3 plus reaction to the test for protein; the sediment contained 0 to 2 red cells per high powered field. The specific gravity was 1.015, the pH was 5.5. The reaction to a qualitative test for urine hemoglobin was strongly positive. A quantitative determination of urine hemoglobin on admission showed 59 mg. per 100 ml., and 4 mg. per 100 ml. on the following day. Examination of the blood revealed a volume of packed red blood cells of 10 per cent, a hemoglobin of 5 gm. per 100 ml., and a white cell count of 35,000 per cu. mm. The differential white cell count was 1.5 per cent blast forms, 2 per cent undifferentiated myelocytes, 7.5 per cent differentiated myelocytes, 25 per cent juvenile neutrophils, 51 per cent segmented neutrophils, 1.5 per cent eosinophils, 7.5 per cent lymphocytes, 2 per cent atypical lymphocytes and 3 per cent monocytes. The platelets numbered 179,000 per cu. mm. There were 7.1 per cent reticulocytes. Slight poikilocytosis and stippling of the red cells was noted,



Fig. 1. Case I. Appearance of scrotal eschar on seventh day after bite.

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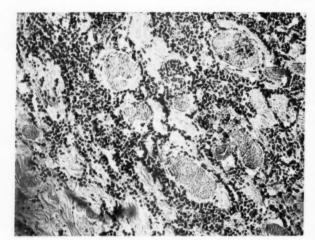


Fig. 2. Case I. Acute inflammatory reaction, with necrosis, involving dartos muscle layer of scrotum.

with moderate anisocytosis and polychromatophilia. A few spherocytes were present, and there was marked erythrophagocytosis involving 5 per cent of the white cells on routine blood smear. There was increased mechanical and osmotic fragility. The reaction to the direct Coombs' test was initially strongly positive. The bone marrow was normal. The result of a test for cold agglutinins was negative, and of a glutathione stability test within normal limits.

The blood sugar was 112 mg., the non-protein nitrogen 53 mg. per 100 ml., the total serum bilirubin was 11 mg. per 100 ml. with 8.5 indirect-reacting pigment. The CO₂ combining power was 21.3 mEq. per L., the serum sodium 130 mEq. per L., the serum potassium 5.4 mEq. per L. Quantitative determinations of plasma hemoglobin showed 126 mg. per 100 ml. on admission and 80 mg. per 100 ml. on the following day. Multiple blood cultures showed no growth. On the second hospital day the reaction to the cephalin flocculation test was 4-plus but results of other liver function tests, including the thymol turbidity, alkaline phosphatase and serum total proteins, were within normal limits. By the third hospital day the urine showed only a trace of hemoglobin, and results of both the direct and indirect Coombs' tests were negative. A single sample of stool contained 425 Ehrlich units of urobilinogen per 100 gm. The roentgenogram of the chest was within normal limits. An electrocardiogram made on admission showed sinus tachycardia with non-specific changes in the T wave.

The patient was given 10 units of packed red cells during the first forty-eight hours, which elevated the hematocrit to 24 per cent. He was also treated with penicillin, streptomycin and prednisolone in amounts as large as 150 mg. daily for a total of five days. The patient maintained a good urinary output. He was febrile for one week. On the tenth hospital day, the scrotal eschar was excised. Histologic examination revealed necrosis of the skin and subcutaneous tissue



Fig. 3. Case II. Appearance of local lesion on eighth day after bite.

with an acute inflammatory reaction extending into the dartos muscle layer. (Fig. 2.) The postoperative course was complicated by the development of a staphylococcal wound infection which responded slowly to therapy with antibiotics and drainage. The patient was discharged much improved on the seventeenth hospital day. The white cell count at that time was 8,550 per cu. mm. with a normal differential count; the hematocrit was 40 per cent.

CASE II. A four year old white girl was admitted to the Vanderbilt University Hospital on November 11, 1958, because of anemia and hemoglobinuria. One day prior to admission she had awakened complaining of a "sore tonsil," and her mother had noted a small red lesion just anterior to the left ear which she interpreted as an insect bite. Although the insect was not identified, the mother stated that there were many spiders in their home. During the day, local pain, swelling and erythema rapidly increased, progressing to ecchymosis with central necrosis. The child became irritable and febrile, and on the evening before admission began to pass dark, "Coca-cola" colored urine. The past and family histories were not relevant. There was no history of previous insect bite, known allergy or blood dyscrasia.

On admission the child was pale, irritable and acutely ill. The temperature was 101°F., pulse 124, respirations 34. There was a large swollen, tender area of ecchymosis involving most of the left side of the face and neck, with erythema extending over the shoulders in a symmetrical distribution. A brownish area of necrosis measuring about 1 by 3 cm. was present in front of the left ear. (Fig. 3.) The left eye was swollen shut. Scleral icterus was present. The liver and spleen were not palpable. The remainder of the physical examination was non-contributory.

The result of the serologic test for syphilis was negative. The urine was very dark and gave a 2 plus reaction for protein. Marked hemoglobinuria was present. Examination of the blood revealed a white blood count of 34,000 per cu. mm. with a differential count of 7 per cent juvenile forms, 64 per cent segmented neutrophils, 20.5 per cent lymphocytes, 2 per cent atypical lymphocytes and 6.5 per cent monocytes. Numerous spherocytes were noted in the peripheral smear. The platelet count was 176,000 per cu. mm., the reticulocyte count 2.3 per cent. The volume of packed red cells was 25 per cent; the hemoglobin was 9.7 gm. per 100 ml. The serum appeared extremely hemolyzed. The serum bilirubin was 2.7 mg. per 100 ml. with 2.3 mg. indirect-reacting pigments. Erythrocyte acetylcholinesterase activity was not significantly depressed.

Because of the possibility that overwhelming sepsis was the cause of the patient's critical condition, penicillin, streptomycin and Chloromycetin® were administered shortly after admission. Blood cultures obtained before treatment showed no growth. Prednisone was also administered in amounts as large as 40 mg. per day for a total of five days.

On the day of admission an exchange transfusion was performed, using 2,000 cc. whole blood, compatible by saline, albumin and indirect Coombs' crossmatching procedures. The patient tolerated this procedure well, and thereafter her condition improved progressively. On the following day the platelet count was 28,000 per cu. mm., the serum uric acid was 9.9 mg. per 100 ml. and the serum potassium was 5.4 mEq. per L. Clinically, however, no generalized hemorrhagic manifestations were noted. On the third hospital day the hematocrit was 27 per cent, and 250 ml. whole blood was administered. The patient maintained a good urinary output throughout her hospital stay, and hemoglobinuria had cleared by the day following the exchange transfusion. She remained febrile for three days and was discharged well on the eighth hospital day. When last seen, two weeks following the injury, she appeared to be in excellent health, and the local lesion had almost completely healed. The hematocrit at that time was 42.5 per cent.

COMMENTS

In 1872 Caveness [1] reported what appears to have been the first recorded example of hemolytic anemia complicating gangrenocutaneous arachnidism. He described a forty-five year old woman who had a large, painful, necrotic ulcer of the thigh resulting from the bite of an insect thought to be a spider. Fever, anorexia and debility ensued, and on the fifth day of her illness jaundice and "copious dark discharges" were noted, suggesting the presence of hemolysis. Jaundice persisted for about one week, but complete healing of the local lesion was protracted. In

1892 Presley [2] reported a similar case. The victim was a seven year old girl who died of anuria on the eighth day of her illness. Although there have been other sporadic reports [14] and reviews [15] concerning necrotic arachnidism in the American literature, no additional cases complicated by hemolysis were published until the report of Gotten and MacGowan in 1940 [3]. In their patient, a three year old girl, methemoglobinuria was demonstrated. A transfusion of 300 cc. whole blood was necessary because of the severity of the anemia, but recovery was complete and otherwise uncomplicated.

In South America, gangrenocutaneous arachnidism has been recognized as a clinical entity since the early reports of Prada in 1896 [16]. Hemolytic anemia was clearly documented as a complication by Mazza [4] in 1908. The ten additional cases which have subsequently appeared in the South American literature are included in Table 1. There is suggestive evidence that hemolysis complicated some of the cases of necrotic arachnidism reported by Costa [17] (Case 2), Macchiavello [16] (Cases 26 and 27) and Landolph [18], but since adequate clinical details are lacking these cases have been excluded. Excellent reviews dealing with necrotic arachnidism have been written recently by Atkins and associates [19] in English and in Spanish by MacKinnon and Witkind [20].

The clinical picture of necrotic arachnidism is characteristic. The local lesion is usually quite painful, although the actual spider bite may occasionally pass unnoticed. Over a three- to seven-day period, local edema, erythema and violaceous discoloration of the skin progresses to circumscribed aseptic necrosis, gangrenous slough and eventual eschar formation. The extent of necrosis is quite variable, but may be alarming, with involvement of subcutaneous tissues down to muscle layers and fascia over a wide area. Healing is characteristically protracted, and painful scars may persist for months or years. Pathologically, the picture is one of an acute, necrotizing inflammatory reaction. When hemolysis occurs, it appears to be a delayed reaction beginning in a matter of hours or, more commonly, from one to five days after the spider bite. Unless death intervenes the hemolytic process is invariably self-limited, usually subsiding within about one week. This should not, however, be construed as a deprecation of the severity of the hemolytic process, for transfusions may be required, as they were in both of our

Table I
SUMMARY OF REPORTED CASES OF NECROTIC ARACHNIDISM WITH HEMOLYTIC ANEMIA

Author and Date	Age (yr.) and Sex	Extent of Necrosis	Hematologic Findings	Urinary Findings (onset and duration of hemoglobinuria)	Jaundice (onset and duration)	Outcome	Comment
Caveness 1872 [1]	45,F	6 by 8 cm. left thigh; painful, slow heal-		"Profuse dark dis- charges"	5th-12th day	Recovered	Insect not identified
Presley 1896 [2]	7, F	3 by 3 cm. left scap- ula, painful	Not examined	"Very dark" 3rd- 8th day, compared to urine of malaria	3rd-8th day	Died 8th day	Died of anuria prob- ably related to therapy with HgCl
Gotten 1940 [3]	3,F	8 by 8 cm. left flank; slow healing	Hemoglobin 59%; red blood cells 2.94 million; white blood cells 17,800	Methemoglobinuria beginning at 48 hr.	Not noted	Recovered	Transfusion 300 cc.
Mazza 1908 [4]	40,M	Large area on left- elbow		Methemoglobinuria	1st-16th day	Recovered	Febrile for 10 days
Mackinnon 1948 [5]	40,F	6 by 6 cm. on arm	Not examined	3rd-6th day	Not noted	Recovered	Blood culture nega-
Mackinnon 1948 [6]	28,F	5 by 6 cm. on arm; slow healing	Not examined	3rd-6th day	3rd-6th day	Recovered	spider positively identified as Lox-osceles laeta
Mackinnon 1938 [7]	9,M	3 by 3 cm. left ear with extensive in- duration face and neck	Not examined	"Hematuria" noted	3rd day	Recovered	Hepatosplenomeg- aly, dubious case
Volpe 1938 [8]	11,M		Blood urea nitrogen 200; serum "red"; methemoglobine- mia	8th-36th hr.	17th-36th hr.	Died 36 hr.	Autopsy performed
Feigues 1935 [9]	32,M	4 by 4 cm. scrotum,	"Anemic"; methe-	1st-7th day	1st-10th day	Recovered	***
Norbis 1948 [10]	7,M	painful Massive involve- ment left arm and chest	moglobinemia Not examined	"Chocolate colored"; methemoglobinuria	Not noted	Died 24 hr.	•••
Costa 1939 [11]	23,F	Left arm; minimal necrosis	Hemoglobin 85%; red blood cells 3.8 million; white blood cells 6,600	"Bile pigments"	3rd day	Recovered	Dubious case
Costa 1939 [12]	42,M	Right shoulder	Red blood cells 1.5	"Intense hemoglo- binuria"	Not noticed	Recovered	***
Costa 1939 [12]	18,M	6 by 8 cm. left arm	Hemoglobin 56%; red blood cells 1.9 million; white blood cells 15,800; hemoglobinemia	Onset at 24 hr.	1st-4th day	Recovered	Transfusion, 200 cc.; antitoxin used
Raffo 1951 [13]	34,M	2 by 2 cm. left pec- toral region, pain- ful	Hemoglobin 6.3 gm.; packed cell volume 21; red blood cells 2.3 mil- lion; reticulocytes 32; white blood cells 18,400; hemo- globinemia; met- hemoglobinemia	Onset on 2nd day	2nd day	Recovered	Well studied case; 6 units blood re- quired; fecal uro- bilinogen 850 mg. %; bilirubin 11.2 mg.; bone marrow
Nance 1960	44,M	6 by 8 cm. scrotum, painful; slow heal- ing		2nd-8th day	4th–8th day	Recovered	10 units packed cells; fecal uro- bilinogen 425; glutathione stabil- ity normal; bili- rubin 11 mg.; bone marrow
Nance 1960	4,F	1 by 3 cm. left cheek, painful	Hemoglobin 9.7 gm.; packed cell volume 25; white blood cells 34,000; hemoglobinemia	2nd-3rd day	2nd-3rd day	Recovered	Exchange transfu- sion; bilirubin 2.7 mg.; red blood cells Acetylcholinester- ase normal

patients. It should also be emphasized that in the pediatric age group, three of five cases reported have terminated fatally [2,8,10].

Opinion has varied as to the exact species of spider responsible for necrotic arachnidism. This has resulted from the fact that the offending arachnid is seldom recovered and often not observed or described with clarity, as was true in our two cases. In only one of the recorded cases of necrotic arachnidism with associated hemolysis was a positive species identification made [6]. The condition was at one time attributed to the bite of Latrodectus mactans, the black widow spider. The present syndrome can be clearly separated from latrodectism, however, by the lack of generalized neuromuscular and autonomic symptoms, and the presence of a severe local reaction progressing to necrosis. Other species that have been considered as likely offenders include Lycosa raptoria [27], Glyptocranium gasteracanthöides [25], Aranea audax [16], and Amaurobius foxis [3].

Macchiavello [23,24] was the first to incriminate Loxosceles laeta as the cause of necrotic arachnidism in South America. He first concluded from epidemiologic evidence that this species was the most likely agent and then confirmed this suspicion by the experimental production of typical cutaneous lesions in guinea pigs. More than a dozen other common species of Chilean spiders, when similarly tested, failed to produce necrotic ulceration. These results were confirmed by Mackinnon [20], who also reported the previously mentioned case in man in which positive species identification was possible.

In this country Atkins and associates [19] showed by similar experiments that Loxosceles reclusus was the agent responsible for necrotic arachnidism in Missouri. It seems clear that the bite of certain members of the family loxoscelidae can give rise to the clinical picture of necrotic arachnidism. Whether other spiders also have this potentiality remains an unsettled question.

The loxoscelidae are widely distributed in the southern part of the United States and South America. Although often referred to as the common "brown spider," the color may vary from yellow or orange to almost black. The spiders are medium-sized, measuring about 8 or 9 mm. in length. The cephalothorax is typically low and flat, and characteristically there is a dorsal

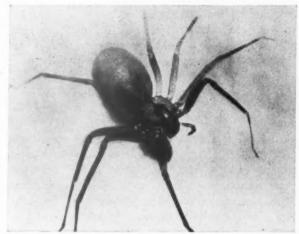


Fig. 4. Loxosceles reclusus. From: Atkins, J. A., Wingo, C. W., Sodeman, W. A. and Flynn, J. E. Am. J. Trop. Med., 7: 165, 1958. [79].

median bar of darker color extending posteriorly from the eyes over the cephalothorax. (Fig. 4.) These spiders are encountered most frequently near human habitations, in cellars, closets and out-buildings. There is no evidence that the spiders are aggressive, and in many of the recorded cases of bites, accidental provocation of some sort seems to have been present.

A number of hypotheses have been proposed to explain the occasional occurrence of hemolytic anemia with necrotic arachnidism. It was at first thought that hemolysis resulted from a direct effect of the venom, analogous to the case of cobra venom in which hemolysis results from the presence of a potent lecithinase which acts by splitting lecithin moieties of the red cell membrane [25,26]. Early studies with spiders showed that hemolysis could be produced in vitro and in vivo using extracts of spider eggs [22] and cephalothoraces [26]. This was taken by some to indicate a general hemolytic property of spider venom [27]. Recently, however, in the more critical studies of Macchiavello [24] and Mackinnon [20], poison gland extracts and actual spider bites were evaluated. It was found that hemolysis could not be produced in any of several species of laboratory animals that were tested. In the case of cobra venom, resistance to hemolysis in certain species such as the ruminants can be related to an absence of lecithin in the red cell stroma. In the camel, on the other hand, an as yet unidentified physiochemical variation in the red cell membrane apparently protects the erythrocyte lecithin from

the action of hemolytic agents [28]. In an analogous manner, hemolysis following spider bite may be due to some subtle variation in the erythrocyte membrane of sensitive subjects.

A large group of drug-induced hemolytic anemias has recently been related to a genetically determined deficit of the enzyme glucose-6-phosphate dehydrogenase within the red cells of sensitive subjects [29]. These cases provide a remarkable example of the manner in which genetic factors may lie dormant for years or even generations, until evoked by a specific environmental challenge. Although deficient glucose-6-phosphate dehydrogenase activity was excluded in one of our patients by a normal glutathione stability test, the possibility remains that hemolysis may be due to a similar enzyme defect, rendering affected cells incapable of detoxifying some component of the spider venom.

Antibodies have been clearly implicated in certain other drug reactions affecting the blood [30,31]. The apparent delayed onset of hemolysis and the initially positive reaction to the Coombs' test in one of our cases are factors which suggest that hemolysis may be due to an immune mechanism. On the other hand, the Coombs' test is not an invariable indication of the presence of antibodies [32]. Serologic studies of sensitive subjects will be required to exclude the possibility that hemolysis is due to an antigen antibody reaction.

A final possibility is that hemolysis may not be directly related to the venom, but rather to a secondary factor such as bacterial toxins or local tissue hemolysins released by the proteolytic action of the spider venom. When blood cultures have been obtained, however, they have been uniformly negative. Although heat-labile hemolysins can be demonstrated in a variety of tissues [33], this explanation fails to account for the low incidence of hemolysis in the population at risk or for the lack of correlation between the extent of necrosis and the occurrence of hemolysis.

Several of the possible mechanisms of hemolysis which have been discussed postulate unusual host sensitivity. It is not known, however, whether all spiders able to cause necrotic arachnidism also have an equal potential for producing hemolysis. Consequently, at present, there can be no rational choice between host sensitivity and vector specificity as an explanation for the rare complication of hemolysis.

SUMMARY

Two cases of acute hemolytic anemia following the bite of unidentified insects are presented. An exchange transfusion was performed in one case, and in the other, multiple transfusions of packed red blood cells were thought to have been life saving. The similarity of these cases to the syndrome of necrotic arachnidism complicated by hemolytic anemia is suggested; evidence that a member of the loxoscelidae is the etiologic agent is reviewed. Further studies are required to elucidate the mechanisms of hemolysis.

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Schistosomiasis Cor Pulmonale*

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In view of the large number of Puerto Ricans now living in the continental United States, schistosomiasis is no longer a disease merely of academic interest. The case to be reported herein represents one of the unusual manifestations of Manson's schistosomiasis, namely, cor pulmonale secondary to an obliterative endarteritis. It is our hope that by reporting this case other patients may be diagnosed and treated before reaching this degree of involvement.

The earliest pulmonary manifestation associated with schistosomiasis occurs when the metacercaria migrate through the lungs, producing, as other parasites do, a Löffler's syndrome. The late pulmonary manifestations of Manson's schistosomiasis are of two types: (1) parenchymatous, with a clinical picture of chronic bronchitis, bronchiectasis or emphysema, and (2) cor pulmonale, which is illustrated by our case [1–3].

The adult parasite lives in the venules of the mesenteric vessels. The female lays eggs at a rate of one to four per day. Some of these eggs find their way into the veins and are carried by the portal circulation to the hepatic venules and sinusoids, provoking reactions of allergic and foreign protein type. Finally, after repeated insults, marked hepatic fibrosis with portal hypertension may develop. Venoarterial shunts around the liver may be responsible for carrying the eggs into the systemic circulation; also embolization of eggs into the lungs from the hemorrhoidal plexus may occur. These eggs in the pulmonary circulation lead to an extensive allergic arteriolitis, with granulomatous reaction around the vessel, which may result in pulmonary hypertension and cor pulmonale.

To our knowledge this is the first case of pulmonary schistosomiasis with cor pulmonale reported in the continental United States.

CASE REPORT

A twenty year old white man (J. R.), a native of Puerto Rico, was admitted to the Temple University Medical Center on October 11, 1959, with a two-year history of dyspnea on exertion and orthopnea. During the year prior to admission the patient had had frequent sore throats, persistent hoarseness, and a chronic cough which was at times productive of blood-streaked sputum. In addition, he also had episodes of syncope on exertion. During the three weeks prior to admission the patient experienced fever, chills, diarrhea and crampy pain in the lower portion of the abdomen. He also noticed shortness of breath at rest and occasionally a bluish discoloration of the lips and nail beds.

There was a history of repeated river bathing in Puerto Rico, followed by generalized itching of the skin. While in Puerto Rico he was found to have schistosomiasis, but was never treated.

The family history was of interest in that a younger brother died in another hospital at the age of sixteen while under treatment for schistosomiasis. Three brothers and two sisters also had been treated for the same disease. Father and mother were repeatedly studied and had normal findings on stool examinations.

Physical examination revealed a small, asthenic, white man in no acute distress. The blood pressure was 110/70 mm. Hg, pulse 110/minute, temperature 98°F. and respirations 24/minute. In the neck a few, small, discrete, non-tender lymph nodes were palpable. The neck veins were distended, with a positive reaction to the abdominal compression test (hepatojugular reflux).

Examination of the heart revealed the point of maximum impulse to be displaced just lateral to the mid-clavicular line and at the fifth intercostal space. There was a prominent systolic pulsation along the left sternal border. Sinus tachycardia of 110/minute was noted. The pulmonic second sound was greater than the aortic second sound, the pulmonic second sound being very loud and sharp. A grade 3 systolic, ejection type of murmur was heard over the precordium, loudest in the third intercostal space and left sternal border, and well transmitted to the neck veins. The chest was symmetric with equal expansion bilaterally. The lungs were clear to percussion and auscultation.

Palpation of the abdomen revealed the liver to be enlarged and somewhat tender; the spleen was 4 fingerbreadths below the left costal margin and very firm. Some cyanosis of the nail beds was present.

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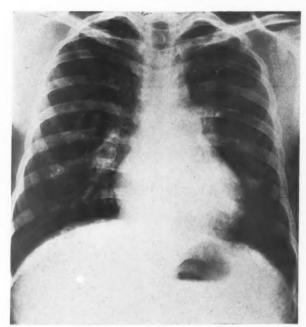


Fig. 1. Roentgenograms of the chest.

There were no petechias or spider nevi. Clubbing of the fingers was not present.

Laboratory findings: Urinalysis was normal, hemoglobin 14.1 gm./100 cc., hematocrit 43 per cent, white cell count 5,100/cu. mm. with 19 per cent eosinophils. The result of a serologic test for syphilis was negative. Stool cultures were negative. Schistosoma mansoni eggs were repeatedly identified in the stools. The serum total protein was 8.7 gm./100 cc., with albumin 3.2 gm./100 cc. and globulin of 5.5 gm./100 cc. The reaction to the cephalin flocculation test was 4 plus in forty-eight hours, thymol turbidity test 21 units, gamma globulin 13.6 units, serum total cholesterol 164 mg./100 cc., serum total bilirubin of 0.8 mg./ 100 cc. with direct fraction of 0.3 mg./100 cc. The serum alkaline phosphatase was 20.8 King-Armstrong units, SGOT 25.6 units, SGPT 19.2 units. The bromsulfalein excretion test showed 7.3 and 6.9 per cent retention at thirty and sixty minutes, respectively. The prothrombin time was 60 per cent of normal and the blood urea nitrogen was 10 mg./100 cc.

Repeated sputum examinations for acid-fast bacilli, fungi and ova of S. mansoni were repeatedly within normal limits. The result of P. P. D. No. 1 test was positive.

A roentgenogram of the chest showed a slightly enlarged cardiac silhouette. (Fig. 1.) On fluoroscopy a prominent pulmonary artery segment was noted and the pulmonary vasculature appeared prominent, especially in the hilar regions. The right ventricle was also enlarged. An electrocardiogram showed right axis deviation, incomplete right bundle branch block and ischemia of the right ventricle. (Fig. 2.)

An electroencephalogram showed a mild degree of

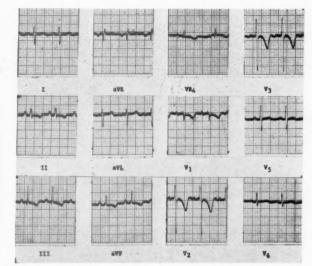


Fig. 2. Electrocardiogram showing normal sinus rhythm, right axis deviation, incomplete right bundle branch block and ischemia of right ventricle (systolic overload pattern).

cerebral dysrhythmia but was otherwise normal. Laryngoscopy revealed paralysis of the left vocal cord.

Pulmonary function tests gave the following results: Respiratory rate 24/minute, minute volume 16.6 L./minute, tidal volume 693 cc., inspiratory capacity 2,850 cc., expiratory reserve volume 1,550 cc. Vital capacity: sitting 3,550 cc. (predicted 4,320 cc., per cent of predicted 82 per cent). Maximum breathing capacity: sitting 64.3 L./minute (predicted 121 L./minute, per cent of predicted 53 per cent). Timed vital capacity: 80 per cent in one second and 100 per cent in three seconds.

Table I
RESULTS OF CARDIAC CATHETERIZATION

Location	Pressure mm. Hg	Vol. % O ₂ /100 cc.
Superior vena cava	4/40	11.3
Right auricle Right ventricle	4/10 57/5	10.7 10.5 11.8
Pulmonary artery	58/31	11.8 11.3
Mean Pulmonary capillary pressure (mean)	8	*

O₂ consumption..... 250 cc./min.

Femoral artery..... O₂ content 16.4 vol. % O₂/ 100 cc. capacity 17.0

96% saturation

Cardiac output..... 5.1 L./min.

Pulmonary arteriolar resistance 517 dynes/sec./cm.⁻⁵
Total pulmonary resistance... 650 dynes/sec./cm.⁻⁵

^{*} No blood could be obtained in the wedge position.

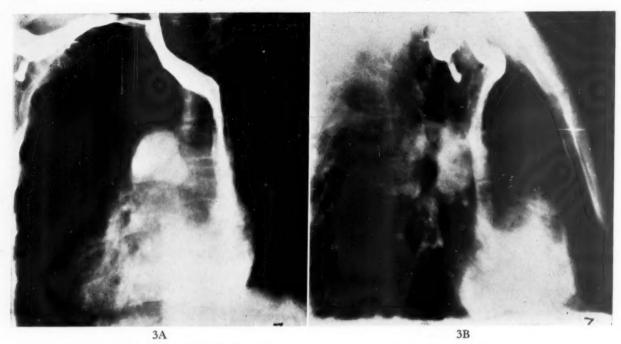


Fig. 3. Angiocardiogram. Note enlargement of the right ventricle and pulmonary artery.

These findings were all within normal limits. However, the moderately reduced maximum breathing capacity may have been due to the patient's lack of comprehension because of language difficulties.

Cardiac catheterization revealed elevated pressures in the right ventricle and pulmonary artery, with a normal pulmonary capillary pressure. Analysis of blood samples obtained at the time of catheterization failed to show the presence of intra- or extracardiac shunts. The cardiac output at rest was found to be 5.1 L./minute and the pulmonary arteriolar and total pulmonary vascular resistance were increased. (Table I.)

A phonocardiogram verified the auscultatory findings already described and the prominent pulmonary component of the second heart sound was suggestive of pulmonary hypertension. Venous angiocardiography showed prolongation of the circulation time of the right side of the heart and intracardiac circulation time. There was definite enlargement of the right ventricle and pulmonary artery. The tertiary pulmonary arterial branches and pulmonary veins appeared normal. The right atrium, left atrium, left ventricle and aorta were normal. These findings were interpreted as compatible with pulmonary hypertension and cor pulmonale. (Fig. 3.)

Needle biopsy specimen of the liver revealed marked portal fibrosis. A biopsy specimen of the lung (Fig. 4, 5 and 6) showed pulmonary firbosis and arteriolar emboli of S. mansoni ova, with secondary granulomatous reaction around the pulmonary arterioles.

The patient responded well to treatment of his mild cardiac failure. In spite of this initial improve-

ment he continued to experience dyspnea and orthopnea on slight exertion, associated with mild cyanosis. He also noted several episodes of chills and fever, during which repeated blood, sputum, urine and stool cultures were negative.

Several days after the open lung biopsy, he experienced chills, fever, marked dyspnea at rest and cyanosis. Leukocytosis was also present. Repeat roentgenograms of the chest were within normal limits. Blood, urine, sputum and throat cultures were repeatedly negative. The patient's condition gradually deteriorated, the right-sided heart failure became worse, and he died five weeks after admission.

Autopsy findings: The body was that of a twenty-one year old white man. Normal amounts of fluids were present in pleural, pericardial and peritoneal cavities.

The heart was markedly enlarged, weighing 430 gm. The right ventricle was seen to take up most of the anterior surface of the heart. It was markedly enlarged and dilated; its wall measured 1 cm. in thickness. The left ventricular cavity was not enlarged and the wall was 1.2 cm. in thickness. There was marked dilatation of the pulmonary artery and at 2 cm. above the pulmonic valve it measured approximately 10 cm. in circumference. The aorta, coronary arteries, inferior and superior vena cava were normal. The valve measurements were all within normal limits.

The lungs appeared heavy and moist. There was fine nodularity of the pleural surface. The cut surface revealed tiny white dots and white streaks which were interpreted as miliary granulomas and probably thickened blood vessels.

The esophagus, stomach and small intestines were grossly normal. The large intestine was noted to have

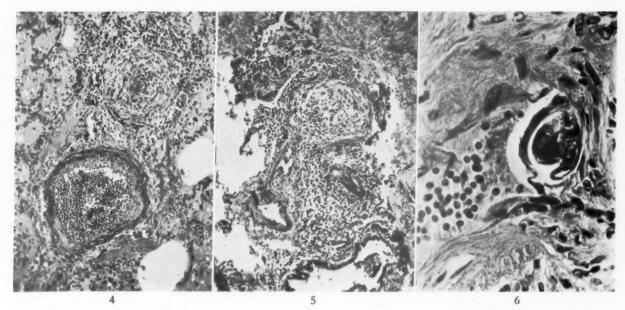


Fig. 4. This low power view of the lung illustrates an occlusion of a pulmonary arteriole. There is marked endothelial and fibroblastic proliferation in the intima and media, and massive infiltration with small round cells throughout the adventitia. These findings are suggestive of pulmonary arteritis. Chronic passive congestion and pulmonary edema are evident in the surrounding alveoli. Original magnification \times 197.

Fig. 5. A longitudinal section through a pulmonary arteriole with segmental, circumscribed panarteritis and perivascular granuloma. Within the latter a schistosoma ovum is visible. The lateral spine in the egg is specific for S. Mansoni. Original magnification \times 160.

Fig. 6. High power view of an ovum being extruded into the wall of the arteriole. An early foreign body reaction is noted. Original magnification × 910.

an atrophic, white and thick mucosa with superficial erosions in the sigmoid. Along the mesenteric border there were firm nodules of grayish white tissue which on section had a pattern suggestive of granuloma formation. These nodules varied from 0.5 to 4.5 cm. in diameter and were more marked along the sigmoid colon.

The liver weighed 1,810 gm. Its capsule was thickened, fibrous, and of a coarse nodular appearance. On sectioning, the liver was very firm, its cut surface was pale yellow, nodular throughout, and showed the typical zoo-parasitic cirrhosis (pipe-stem cirrhosis) with thickened sclerotic portal veins surrounded by fibrous tissue and an outer pale yellow rim of liver parenchyma.

The spleen weighed 430 gm., was markedly enlarged, firm and suggestive of chronic passive congestion.

The remainder of the postmortem findings was noncontributory. The microscopic findings are illustrated in Figures 4, 5 and 6.

COMMENTS

This patient presented the classic picture of pulmonary hypertension. The dyspnea and episodes of syncope on exertion were manifestations of a decreased cardiac output, even when, as with our patient, the cardiac output at rest was normal. The hoarseness was attributed to paralysis or paresis of the left vocal cord as the result of compression of the recurrent laryngeal nerve by the dilated pulmonary artery. Cyanosis usually appears during the terminal stages, when the failing right ventricle is unable to overcome the obstruction present in the pulmonary arterioles. In some patients, in whom large numbers of pulmonary arteriovenous fistulas are present, cyanosis may occur at an early stage [4,5].

The physical findings, characterized by the absence of emphysema or clubbing of the fingers, the presence of pulsation along the left sternal border, the accentuated sharp pulmonic second sound and the systolic ejection murmur, were all manifestations of pulmonary hypertension with an enlarged right ventricle. This was verified by angiocardiography.

Of interest is the finding of relatively normal pulmonary function in a patient who showed so much dyspnea on slight exertion. The cardiac catheterization helped elucidate the pathophysiology by demonstrating elevated right ventricular and pulmonary artery pressure with a normal pulmonary capillary pressure, all of which were indicative of a precapillary obstruction. Finally, the lung biopsy specimen showed the embolic ova in the pulmonary arterioles, with endothelial proliferation and the granulomatous reaction around the vessel.

This patient was not treated with Fuadin® since his condition was believed to be so critical that the side effects of the drug might have proved fatal. Moreover, the hepatic and pulmonary changes appeared to be irreversible. Early diagnosis and treatment of schistosomiasis may arrest the disease process and prevent such fatal complications, even in the presence of early hepatic or pulmonary lesions [6]. This is even more important when the patient is no longer in the endemic area and reinfection is not possible.

SUMMARY

A case is reported of a twenty-one year old white Puerto Rican man, known to have schistosomiasis since childhood. The clinical picture presented was that of cor pulmonale. Pulmonary function was found to be normal. Cardiac catheterization and venous angiocardiography disclosed findings consistent with an obstructive lesion of the pulmonary vascula-

ture. Lung biopsy and finally postmortem examination established the diagnosis.

Acknowledgment: We are indebted to Dr. M. A. Hennesy, Temple University Medical Center, who performed the autopsy and to Dr. George B. Morales of Providence Hospital, Washington, D. C., for reviewing the microscopic findings.

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Histiocytic Medullary Reticulosis*

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THE classification of hyperplastic and neoplastic disease of the lymphoreticular tissue proposed by Robb-Smith [1] has met with little recognition outside England. Thus, it is not surprising that histiocytic medullary reticulosis, a malady sharply delineated clinically and pathologically, has undeservedly escaped attention as a separate disease. Recently a patient with this disorder, in whom thorough hematologic studies were performed was examined at autopsy; the findings form the basis of this report.

CASE REPORT

A seventy-eight year old white man was admitted to The Mount Sinai Hospital on January 28, 1959, with anorexia, weakness, jaundice, hepatomegaly and splenomegaly. He had been well until the onset of symptoms. In the six weeks prior to admission he had lost 12 to 15 pounds. After three weeks he noted light stools and dark urine, but experienced no pain or pruritus. The patient had taken no drugs other than antacids and aspirin, and there was no history of exposure to jaundiced persons. Physical examination revealed a well nourished, elderly man in no distress. Positive findings included slight icterus, enlarged, soft and non-tender supraclavicular and axillary nodes, enlarged liver and spleen, and pitting edema of the ankles and feet.

The urine specific gravity varied between 1.020 and 1.024, with traces of protein. On admission the reaction of the urine sugar test was 4 plus, and mild glycosuria was found on repeated examinations. Bile and urobilinogen in dilutions of 1:160 were present in some urine specimens. Variable but small numbers of red cells, white cells and casts were noted regularly. The stool guaiac test showed 2-plus blood. The blood urea nitrogen was 34 mg. per cent, blood sugar 142 mg. per cent, serum albumin 3.3 gm. per cent and globulin 2.3 mg. per cent, cholesterol 210 mg. per cent, cholesterol esters 140 mg. per cent. The result of the cephalin flocculation test was 2 plus, thymol turbidity test 1 unit, bromsulphalein retention 14 per cent. The serum activity of glutamic-oxalacetic transaminase was 36 units. The prothrombin time was 17.5 seconds, with a control of 13 seconds. Serum

electrophoresis showed all components but alpha₁ globulin to be low. Mucoproteins were 123 mg. (normal 48 to 75 mg.) per 100 ml. serum. Zinc sulfate turbidity was 3.2 units (normal 4 to 8 units). The serum bilirubin was 1.2 mg. with 0.6 mg. per 100 ml. direct reacting; one week later it rose to 2 mg. with 1.6 mg. direct reacting. The serum alkaline phosphatase was 24.6 King-Armstrong units initially and rose to 40.4 units. The erythrocyte sedimentation rate was 10 mm, per hour.

On hematologic examination (Table 1) some hypochromasia, anisocytosis and a few spherocytes were noted. The osmotic fragility of red cells was normal, the result of the mechanical fragility test was positive at 8.4 per cent saline solution, with a control of 3.8 per cent. The marrow (Table 1) was hypercellular, with increased megakaryocytes. Erythropoiesis and granulopoiesis were active, and no tumor cells were seen. Many blood cultures were negative. Proteus was grown from the urine. A liver biopsy specimen showed portal infiltration and fibrosis, with destruction of the lobular periphery. Around the portal tracts atypical histiocytes surrounded and replaced necrotic liver cells. Roentgenogram of the chest revealed bilateral emphysema, blunting of the right cardiophrenic angle, a normal-sized heart and an elongated and tortuous aorta. An electrocardiogram was normal.

In the hospital the patient had almost daily chills and temperature spikes from a baseline of 100° up to 105°F. He was given several blood transfusions, chloral hydrate, penicillin, streptomycin, Ilosone, Kantrex, Diamox, Diuril and Compazine. By the end of the first week he became drowsy and his appetite decreased greatly. He also became quite short of breath. A flapping tremor and fetor hepaticus developed during the second week, and he became comatose and hypotensive. Nuchal rigidity was detected as well as bilateral basilar rales. The liver and spleen increased somewhat in size. The patient's temperature rose to 106.2°F., and after two days of coma he died on the fifteenth hospital day, after two months of illness.

At necropsy, while the superficial nodes were not enlarged, those of the mediastinum, retroperitoneum and the lesser omentum were. These nodes were discrete, soft and uniformly grey-white. Grossly, they failed to show evidence of necrosis, hemorrhage or fibrosis. The liver was enlarged (2,680 gm.). The

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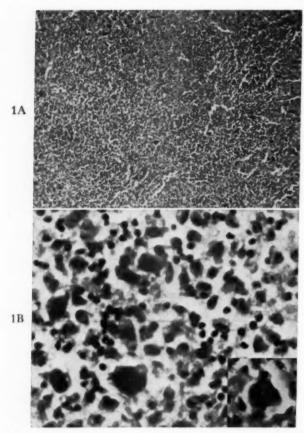


Fig. 1. A, low power view of lymph node. Hematoxylin and eosin stain, original magnification × 100. B, lymph node showing many histiocytes and a giant "prohistiocyte." Hematoxylin and eosin stain, original magnification × 640. Insert, multinucleated giant cell resembling Reed-Sternberg cell. Hematoxylin and eosin stain, original magnification × 640.

portal tracts were widened to form a grey network. Numerous small, reddish areas, up to 0.5 cm. in diameter, were noted. The spleen was fleshy and strikingly enlarged (850 gm.), with a homogeneous deep red cut surface displaying bulging nodules measuring up to 3 cm. The follicular and trabecular landmarks were obliterated. The bone marrow was red, moist and of normal consistency. The duodenal mucosa was focally eroded immediately distal to the pylorus. The brain was not examined.

On microscopic examination the architecture of the lymph nodes (Fig. 1A) was almost unrecognizable because of a proliferation of histiocytic elements, of which three types could be distinguished. (Fig. 1B.) The predominant type had a pale, vesicular, elongated nucleus and abundant eosinophilic cytoplasm. Some of these cells contained engulfed red cells. Occasional giant cells, similar in appearance to Reed-Sternberg cells, could be found. The third type was a cell about 10 to 15 μ in diameter with eosinophilic cytoplasm and a large, deeply basophilic nucleus, which was frequently twisted or folded (prohis-

TABLE I HEMATOLOGIC STUDIES

	Admis- sion	First Week	Second Week
Hemoglobin (gm. %)	9.4	8.5	9.0
Red blood cells (million/cu. mm.)		3.92	3.57
White blood cells (per cu. mm.)	4,300	2,300	2,950
Segmented cells (%)	22	48	26
Band forms (%)	54	44	41
Lymphocytes (%)	23	4	32
Monocytes (%)	1		1
Atypical lymphocytes (%)		4	
Reticulocytes (%)		1.2	1.5
Platelets (per cu. mm.)		198,000	144,000
Mean corpuscular volume (µ3)		85	76
Mean corpuscular hemoglobin (μμg.)		37	24
Mean corpuscular hemoglobin content (%)		32	31.5

Bone Marrow. Per cent of Cells

Myeloblasts	0.5	Eosinophils	2.5
Promyelocytes			
Neutrophilic myelocytes	23.5	Plasma cells	0 5
Eosinophilic myelocytes	2.0	Reticulum cells	1.0
Neutrophilic metamyelocytes	18.0	Proerythroblasts	1.5
Neutrophilic band forms	9.5	Erythroblasts	7.5
Neutrophilic segmented cells	3.5	Normoblasts	23.5

tiocyte of Bodley Scott and Robb-Smith [1]). In a few areas pre-existing follicles could barely be made out. Small lymphocytes were uniformly interspersed among the proliferated histiocytes. In the larger sinuses collections of polymorphonuclear leukocytes, mobilized, frequently phagocytic histiocytes and coagulated protein were found. With silver impregnation of the reticulum fibers the normal lymph node architecture was more clearly outlined. The fibers were delicate and not increased in number.

The spleen (Fig. 2A) was massively infiltrated by histiocytes with small nuclei and large eosinophilic cytoplasm, usually containing many phagocytosed and lysed red cells. (Fig. 2B.) Occasional prohistiocytes and giant cells were present. Masses of erythrophagocytic histiocytes showing scant reticulum fibers protruded into the dilated sinusoidal veins. (Fig. 2C and 2D.) Proliferated histiocytes were found within Billroth's cords as well as within the sinusoids. While these cells showed moderate staining with the periodic acid-Schiff reaction, they did not stain with Alcian blue, nor did they contain lipids (osmic acid). The sinusoidal lining cells were frequently recognizable and appeared normal. In many areas these littoral cells were absent. As in the lymph nodes, the follicles had for the most part disappeared, and the few remaining were atrophic. The reticulum fibers were delicate and their architecture was mostly well preserved.

In the liver, the portal tracts were widened and infiltrated by histiocytes and their precursors. (Fig. 3A.) Variable and irregular destruction of the limiting plate was seen. The bile ducts were not amputated. Numerous foci of necrosis, occasionally hemorrhagic,

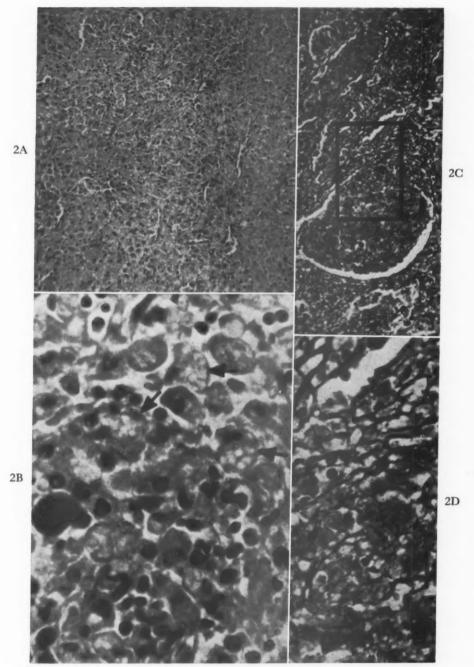


Fig. 2. A, low power view of spleen. Hematoxylin and eosin stain, original magnification × 160. B, spleen infiltrated by many erythrophagocytic histiocytes (arrows). "Prohistiocyte" at left of picture. Hematoxylin and eosin stain, original magnification × 640. C, mass of phagocytic histiocytes, showing scant reticulum fibers, protruding into blood vessel. Gomori's silver impregnation, original magnification × 160. D, high power view of boxed area showing reticulum framework of histiocytes in blood vessel. Original magnification × 640.

were scattered throughout the parenchyma. Large numbers of lymphocytes and a few polymorphonuclear leukocytes were present in the portal tracts and in the vicinity of the necrotic areas. Moderate regenerative activity was characterized by large, frequently binucleated cells and by thickened plates. Slight periportal fatty infiltration was present. The Kupffer cells were enlarged, bulging and displayed erythrophagocytosis.

The bone marrow in some areas was very cellular.

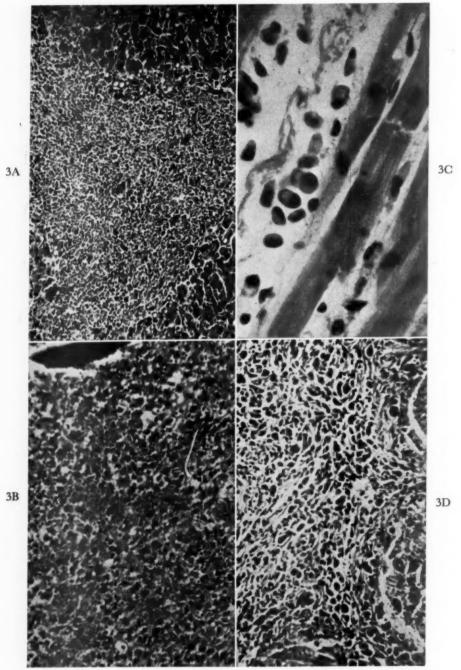


Fig. 3. A, liver showing infiltration of portal tract with histiocytes. Hematoxylin and eosin stain, original magnification × 100, B, bone marrow with sheets of histiocytes and scattered lymphocytes. Hematoxylin and eosin stain, original magnification × 100. C, histiocytic infiltration of myocardium. Hematoxylin and eosin stain, original magnification × 640, D, epididymis with large area of histiocytes. Cytoplasm of these cells appears dark due to phagocytosed pigment. Hematoxylin and eosin stain, original magnification × 160.

It exhibited active erythro- and myelopoiesis. In other areas the marrow was markedly congested but rather depleted of nucleated cells. Most of these were reticulum cells, frequently showing engulfed nuclei or erythrocytes. Large foci consisting of sheets of histiocytic cells were scattered throughout the marrow. (Fig. 3B.) No increase in or condensation of reticulum fibers was noted.

Histiocytic infiltration of the heart (Fig. 3C), pancreas, pylorus and epididymis (Fig. 3D) was noted.

Hemo- Blood Blood Cells (%) (cu. mm.)	mal	,	neutrophils Low plate	mal			mal		13% monocytes Low platelets	mal	eased neutro-	ymphocytes	nectomy	:	tic anemia	White blood cells de-	THE STATE OF THE PARTY OF THE P	mustard therapy	utrophils			нн	l l	HH	H 6	11 61
White Blood Cells (cu. mm.)	6,600 Normal		1,800 16.5%			7,100	2,200 Normal		1,000 13%	1,900 Normal	17,800-7,600 Increased neutro-	2,500-200 869			e e e	13,200			000,6	9,000	9,000 3,500 8,200	9,000 3,500 8,200 5,600	9,000 3,500 8,200 5,600	9,000 3,500 8,200 5,600 12,200 1,300	9,000 3,500 8,200 12,200 1,300 5,800	9,000 3,500 8,200 12,200 1,300 5,800 2,000
Hemo-globin (%)	69		30	55	37	89	98	53	50			49		:	32	7.7 gm.			7.6 gm.	7.6 gm. 5 gm.	7.6 gm. 5 gm. 66	7.6 gm. 5 gm. 66 56	7.6 gm. 5 gm. 66 56 18.5	7.6 gm. 5 gm. 66 56 18.5	7.6 gm. 5 gm. 66 56 18.5 64 88	7.6 gm. 5 gm. 66 56 18.5 64 88 49
Spleno- megaly	+		++	++	+	+	+	+	+	+	+	+		:	+	+			+	+1	+11	+111	+111+	+111++	+111+++	+111++++
REPORTED CASES Hepato-Spleno-megaly megaly	1		ı	:+	+	+	+	+	+	+	1	+		:	+	+			I	1.1	1 1 1	1111	1 1 1 1 +	1111++	1111+++	1 1 1 1 ++++
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Dura- tion (mo.)	2		٠, ٠	· 10	41%	1	2	00	21/2	6	7	15	,	0	13	_			12	12	12 4 21%	12 4 4 3 2 1/2	12 23/2 0	12 4 4 3 23/2 7	12 4 4 2,1/2 0 7 1	12 23/2 0 11/3
Year, Age (yr.)	1928,63,M		1929,69,F	1933,39.M	1934,65,F	1934,26,F	1939,48,F	1939,31,M	1939,41,M	1939,52,M	1944,52,F	1946,35,F	2004	1,72,1661	1952,66,F	1953,56,F			1953,30,F	1953,30,F 1953,41,M	1953,30,F 1953,41,M 1956,55,M	1953,30,F 1953,41,M 1956,55,M 1956,59,M	1953,30,F 1953,41,M 1956,55,M 1956,59,M 1956,37,M	1953,30,F 1953,41,M 1956,55,M 1956,59,M 1956,37,M	1953,30,F 1953,41,M 1956,55,M 1956,59,M 1956,37,M 1956,27,M	1953,30,F 1953,41,M 1956,55,M 1956,59,M 1956,37,M 1956,27,M 1956,55,M
Author	Tschistowitsch,		Bykowa [3]			[7] uo		Robb-Smith [1]			Anderson [8]	Asher [9]		Thompson [10]	Willcox [17]	Israels [72]					Marshall [73,14]	Marshall [13,14]	Marshall [13,14]	Marshall [73,74]	Marshall [13,14]	Marshall [13,14]

The iron-free pigment normally occurring in the epididymis was found within the histiocytes. No organs showed fibrosis, increased reticulum or pronounced iron deposition; in fact, stainable iron was strikingly decreased despite the impressive erythrophagocytosis.

COMMENTS

Cases of histiocytic medullary reticulosis had, of course, been reported prior to the study of Bodley Scott and Robb-Smith [7]. Dameshek [5] in a comprehensive review in 1933 presented a case of this disorder as aleukemic reticulosis and surveyed the pertinent literature, although he included what later became known as Letterer-Siwe's disease. The case reported by Beaver and Johnson [7] and the unpublished case by Berglund [15] are additional observations from this country.

A review of the twenty-five previously published cases (Table II) reveals that survival after the onset of symptoms varied from one month to fifteen months, with a median duration of five and a half months. In those cases for which data are given, 92 per cent of the patients had anemia, 88 per cent had splenomegaly, 70 per cent displayed hepatomegaly, 73 per cent showed purpura and 55 per cent were jaundiced. Only one patient had no fever. The patients ranged in age from twenty-six to seventy years, with a median age of forty-eight. No sex predominance was present (thirteen men and twelve women). Splenectomy may offer a short respite [9]. Hemolytic anemia has been reported [11]. In our case the red cells were microcytic and normochromic, and a slight hemolytic component was suggested by the increased mechanical fragility.

The microscopic picture is dominated by diffuse proliferation of histiocytes and their precursors in lymph nodes, spleen, portal tracts of the liver, bone marrow and various other organs. Tumor formation, as seen in lymphomas, is absent. These cells show phagocytic properties, most strikingly in the spleen, where massive erythrophagocytosis is usually present. The infiltrate invariably shows scattered giant cells, some of which are identical with those seen in Hodgkin's disease This explains why cases of histiocytic medullary reticulosis have been misdiagnosed as "atypical" Hodgkin's disease [1]. However, eosinophils, plasma cells and fibrosis are invariably absent. In addition, patients with Hodgkin's disease usually exhibit a more protracted course and ordinarily respond, at least temporarily, to treatment.

Until Letterer-Siwe's disease emerged as an independent disease entity instances of this disorder were confused with the malady under discussion. In both diseases there is a generalized proliferation of phagocytic histiocytes, with a similar inexorable course. However, Letterer-Siwe's disease is almost always accompanied by striking skin lesions and characteristically occurs at a different age. The course of the disease may be prolonged by treatment. In the absence of a known causative agent, both histiocytic medullary reticulosis and Letterer-Siwe's disease should be considered as representatives of a non-leukemic diffuse histiocytic proliferative disorder.

SUMMARY

The case presented fulfills the clinical and morphologic requirements of histiocytic medullary reticulosis as laid down by Bodley Scott and Robb-Smith [1]. This invariably and apparently rapidly fatal disease of adults is characterized morphologically by a diffuse proliferation of phagocytic histiocytes and their precursors in lymph nodes, spleen, liver, bone marrow and other organs. The striking erythrophagocytosis, particularly in the spleen, is diagnostic. Wasting, fever, moderate lymph node enlargement, hepatosplenomegaly, hypersplenism and icterus are found.

ADDENDUM

Since submission of this article, Yü Chih-Fei et al. [16] have reported a series of eighteen cases in which the diagnosis, based on bone marrow aspiration, was histiocytic medullary reticulosis. In four cases the diagnosis was verified at autopsy.

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Primary Rhabdomyosarcoma of the Heart and Complete Atrioventricular Block*

A Case Report and Review of the Literature

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Primary tumors of the heart, although rare [1], frequently lead to atrioventricular conduction defects [2]. The present case concerns a patient with a primary rhabdomyosarcoma of the heart in whom the predominate manifestation was complete heart block. Although electronic cardiac pacemakers have been used previously in patients with complete heart block [3,4], we believe that this is the first patient with a primary cardiac neoplasm in whom it has been employed. Of equal interest is the evolution of this patient's clinical picture.

CASE REPORT

One year prior to admission to the University of Oregon Medical School Hospital, while painting, the patient, a forty-one year old white man, experienced the abrupt onset of transient, oppressive substernal pain associated with dyspnea and diaphoresis. He consulted his family physician who concluded, after physical examination, a blood count and electrocardiograms, that there was no evidence of heart disease. Eight months after the appearance of these symptoms he was referred to a cardiologist because of the persistence of exertional dyspnea with chest pain. At this time, first degree heart block and an erythrocyte sedimentation rate of 80 mm. at forty-five minutes (normally 15 mm. or less at forty-five minutes, Wintrobe) were present. Cardiac fluoroscopy failed to demonstrate any abnormalities and the cardiothoracic ratio was 40 per cent. Once again, no definite evidence of cardiac disease could be found.

However, the patient's symptoms continued with increasing frequency and two weeks prior to admission he had his first episode of lightheadedness. At this time he became aware of the slow, forceful nature of his heart beat. All his symptoms became more severe and the night prior to admission he was seen at home

by a physician and a diagnosis of complete heart block was made. At this time his faint feeling was promptly relieved by the sublingual administration of Isuprel® (isoproterenol). He denied orthopnea, cough or dependent edema with this illness; however, he had awakened with sharp chest pain and shortness of breath on three occasions the week prior to admission.

He had not had a recent infection of the respiratory tract or other febrile illness and denied skin rash, arthralgia or arthritis. There was no family history of cardiac disease. The system review was non-contributory.

The patient was obviously apprehensive about his slow heart rate. His chest was clear to auscultation and percussion. There was a forceful apical impulse palpable in the fifth left intercostal space at the anterior axillary line. Lower sternal dullness without an accompanying thrust was present. The apical rate varied between 30 and 45 per minute with fluctuations in the intensity of the first heart sound. Occasionally, a third heart sound was audible in mid-diastole with the patient in the left lateral decubitus position. A "cannon" wave was irregularly present in the neck veins. Splitting of the second heart sound was present, with the aortic component louder than the pulmonic. A soft, mid-systolic (left-sided ejection) murmur was heard along the left sternal border at the third and fourth intercostal spaces without transmission to the neck. There was no adenopathy. The remainder of a complete examination was within normal limits.

The electrocardiogram on admission demonstrated complete heart block with an idioventricular pacemaker. Although the patient's history was consistent with coronary artery disease and possible myocardial infarction, the presence of an elevated sedimentation rate for approximately three months posed the question of myocarditis. There was definite evidence of left ventricular hypertrophy and dilatation by physical findings and x-ray examination. Cardiac fluoroscopy failed to demonstrate any signs of pericardial effusion.

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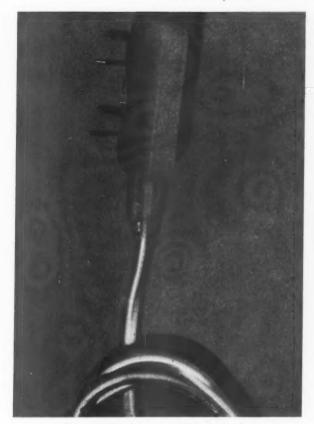


Fig. 1A. Roth myocardial electrode.

At the time of hospital entry the patient was given Isuprel sublingually and the cardiac impulse was monitored by an Electrodyne pacemaker. Because of the possibility of either myocardial infarction or myocarditis, Indon® (phenylindandione) and prednisone therapy was instituted. After approximately six weeks of prednisone therapy, three weeks at 45 mg. per day and three weeks at 60 mg. per day, it was apparent that no satisfactory improvement had occurred since the inherent heart rate remained at approximately 30 per minute without Isuprel. The erythrocyte sedimentation rate remained elevated (average of 70 mm. at forty-five minutes, Wintrobe) during steroid administration as did the C-reactive protein (average 3 plus). The white cell count remained within the normal range. A trial of parenterally administered gamma globulin produced no alteration in his clinical state.

Six weeks after admission, the cardiology staff recommended the implantation of myocardial electrodes to prevent the syncope and motor seizures which the patient experienced when his heart rate fell below 30 per minute. Such a recommendation was based on the patient's apparent refractoriness to Isuprel therapy.

Through a left thoracotomy incision, two pacemaker electrode wires were inserted into the free wall of the right ventricle. At this time it was noted that

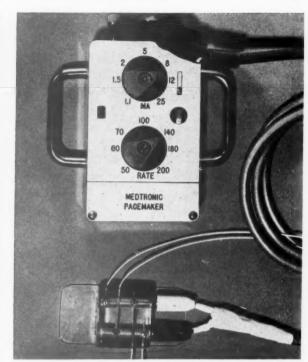


Fig. 1B. Transistorized pacemaker apparatus used in this case. In the lower part of the photograph is shown a light-weight plastic junction box which enables interchange of myocardial electrodes without interrupting the circuit. Also, a new source of current can be added without interruption of stimulation. The plastic flanges allow skin application by adhesive tape.

the myocardium appeared edematous and gray. A biopsy of the myocardium of the right ventricle was technically unsatisfactory even though the appearance of the heart at surgery strongly suggested a diagnosis of myocarditis. The initial electrodes remained in place for approximately six weeks and during this interval the patient's heart rate was maintained at 60 to 70 per minute. No appreciable change in the enlarged cardiac silhouette occurred with the increased heart

Ultimately the original pacemaker wires lost contact with the myocardium, and when percutaneous insertion of new electrodes proved unsuccessful a thoracotomy was again undertaken. Four pacemaker wires were sutured into both the myocardium and pericardium. The appearance of the cardiac muscle was unchanged. Because of the difficulty in achieving hemostasis at the time of his first biopsy, another biopsy was not performed. During the week preceding his second thoracotomy, peripheral edema and hepatomegaly appeared and were considered to be manifestations of congestive heart failure. He was given oral digitalis without detectable improvement. Sodium restriction to 0.5 gm. per day, which had been initiated at the time of corticosteroid administration, was continued and Mercuhydrin® (meralluride) therapy resulted in a transient diuretic response.



Fig. 2. Right atrium and ventricle. The area of A-V node (AV) is replaced by large tumor nodule. Note marked narrowing of the superior vena cava by tumor.

After three weeks the second set of electrode wires broke at the site of entry into the myocardium and necessitated a third thoracotomy. At this point a Roth electrode (Fig. 1A) was implanted into what was believed to be the free wall of the left ventricle near its outflow tract. Prednisone therapy was stopped at this time, after a gradual reduction of dosage, but within one week he complained of vague burning postprandial epigastric distress. Prophylactic milk and antacids had been used during steroid treatment, and their frequency was now increased to an hourly schedule, with definite improvement in his symptoms. An upper gastrointestinal series did not show any abnormalities of the esophagus, stomach or duodenum. Following the third thoracotomy the heart rate was stabilized, using a small, transistorized pacemaker (Fig. 1B) and he was discharged to his home.

Two weeks after discharge he was seen in the Outpatient Clinic because of weakness, exertional dyspnea, dependent edema and recurrent burning, nocturnal epigastric distress relieved by the ingestion of milk and antacid therapy. During this visit two 1 cm., rocky hard, freely movable nodes were palpable in the left side of the neck at the angle of the mandible and the clavicular insertion of the sternomastoid muscle. On his next visit to the clinic splenomegaly

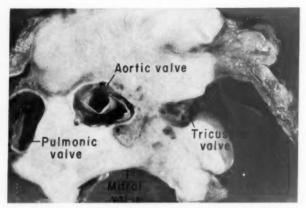


Fig. 3. Transverse section through the heart, slightly superior to the annuli fibrosi. The interatrial septum as well as the myocardium are replaced by tumor. The nodular mass protruding into the tricuspid area represents tumor replacement of the A-V node.

was noted for the first time. Nausea and vomiting, which were aggravated by the ingestion of milk, had been present for two days. His epigastric pain was now only partially relieved by antacid therapy. Because of the increase in his symptoms and the obvious severity of his clinical state, he was readmitted to the University of Oregon Medical School Hospital.

Additional findings at this time were lymphadenopathy of the left axillary gland, a Virchow's node, and a large osteolytic lesion of the seventh left posterior rib. His course in the hospital was one of inexorable deterioration and he died three days after admission.

At postmortem examination the pericardium was obliterated and had to be dissected free from the epicardial surface. The heart was immense, weighing 1,850 gm., and a tumor was found to involve the right and left atria, the area of the A-V node being completely replaced by neoplastic tissue. (Fig. 2.) Further dissection showed the tumor to involve all four of the valve rings (Fig. 3), the superior vena cava (the orifice of the vessel measured 7 mm. in diameter), the orifice of the coronary sinus and the right superior pulmonary vein. The Roth electrode was encased in fibrous tissue, the positive electrode was embedded in the pulmonary artery just above the valve annulus and the negative pole over the right ventricular outflow tract. Metastatic tumor was found in cervical, mediastinal and mesenteric lymph nodes, the pancreas, liver, adrenals, thyroid, stomach, pericardial sac, myocardium of the ventricles, the right fifth rib, and left seventh, eighth, tenth and eleventh ribs and the upper lobe of the right lung. Interstitial pancreatitis was present due to obstruction of the pancreatic duct by metastatic tumor.

In addition to hyperemia and edema of the lungs, multiple fibrous adhesions of the pleura were present at sites of previous thoracotomies. Bilateral hydrothorax, 600 ml. on the right side and 800 ml. on the left side, was evident. Passive congestion of the liver

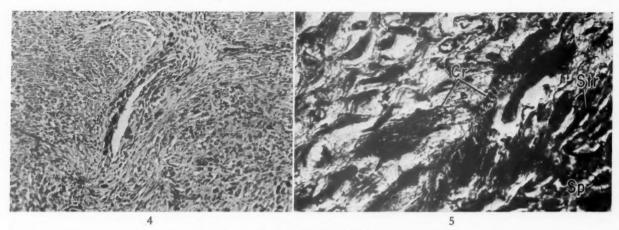


Fig. 4. Tumor metastasis involving the interventricular septum displaying invasion of myocardium and a capillary. Original magnification × 100.

Fig. 5. Section from primary tumor site showing rhabdomyoblasts. (Note cross-striation (Cr), spider web cells (Sp) and strap cells (Str).) Vacuolization of cytoplasm and longitudinal myofibrils are present. Phosphotungstic acid-hematoxylin stain, original magnification \times 1,275.

and spleen and 1,000 ml. of ascitic fluid were encountered on opening the abdomen.

The primary tumor, as well as the metastases, was composed of highly pleomorphic, anaplastic cells displaying no characteristic growth pattern. (Fig. 4.) Spindle cells, strap cells, spider web cells and completely undifferentiated cells were noted, the latter including numerous bizarre, often multinucleated giant cells. Longitudinal myofibrils were readily demonstrated. Phosphotungstic acid-hematoxylin stain brought out several strap cells and tumor giant cells displaying cross striation. (Fig. 5.) Vacuolization of the cytoplasm, presumably due to glycogen, was a prominent feature. Mitotic and atypical mitotic figures were frequently encountered.

The final diagnosis was rhabdomyosarcoma of the atria with metastases to the cervical, mediastinal and mesenteric lymph nodes, pancreas, liver, adrenals, thyroid, stomach, pericardium, ventricular myocardium, ribs and right lung.

COMMENTS

Primary tumors of the heart are rare. In 1934 Lymburner [5] assembled 226 cases of primary benign and malignant cardiac tumors from the literature and by 1945 these had increased to 329 [6]. In 1949 Whorton [7] summarized all reported cases of malignant neoplasm originating in the heart, amounting to 100. Two years later this total was increased to 113 cases by Pritchard [8] and by 1955, 143 cases were in print, according to Brucker and Glassy [9]. Table 1 includes what we believe to be all the reported cases of rhabdomyosarcoma [10–38].

The infrequent occurrence of primary heart vol. 31, NOVEMBER 1961

tumors can be appreciated when one realizes that they are found once in every 5,000 unselected autopsies [1]. When compared to metastatic tumors of the heart, this is even more striking since the latter are twenty to forty times as frequent [8] and occur in approximately 20 per cent of all patients dying with neoplastic disease [39,40].

The presence of an atrioventricular conduction defect is stated to be more common in cardiac neoplasm than any other form of arrhythmia [2,42]. Obscure and intractable heart failure should always suggest the possibility of a cardiac tumor [41,43]. Cardiac enlargement, which was a prominent feature of this case, did not show the irregularities of the cardiac borders which have been commented upon previously [44]. Initially, the widened cardiac silhouette (Fig. 6) was suspected to be the result of the marked bradycardia; however, when the size did not diminish after an electrically induced increase in his heart rate this idea was abandoned. Pericardial effusion, which is common in cases of cardiac malignancy (Table 1), was not present in this patient. There was no clinical evidence of major venous channel obstruction. In many ways the diagnosis of cardiac malignancy was obscured by our therapy. The cervical adenopathy initially was considered to be the result of repeated thoracotomies. The epigastric distress was thought to be a sequel of prednisone therapy. It was only after the steady deterioration of the patient's clinical state and the appearance of rapidly increasing

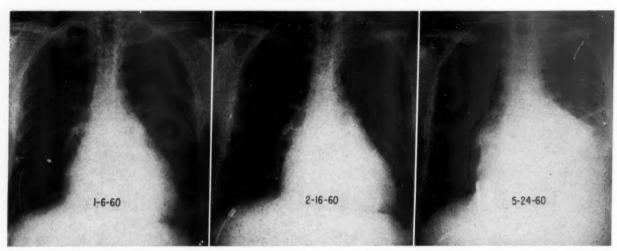


Fig. 6. Representative chest roentgenograms. The roentgenogram on the left was obtained one week before insertion of first pacemaker wires. Worthy of notice is cardiomegaly with smooth contour. The center roentgenogram shows no appreciable diminution in cardiac size following one month of pacemaker stimulation at a normal rate. The roentgenogram on the right shows change commensurate with three left thoracotomies. The heart size has definitely increased and the right atrial contour is irregular.

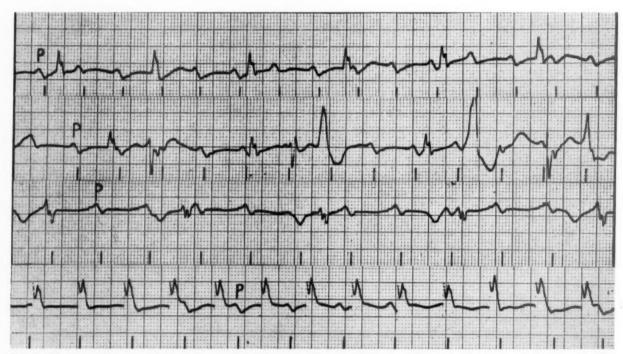


Fig. 7. Electrocardiograms during surgery for placement of pacemaker wires. The ventricle lines at bottom of strips indicate the atrial rates. First row, complete A-V block A:125; V:52; the patient was receiving Isuprel. Second row, the rate of infusion of Isuprel increased. Third row, Isuprel infusion stopped A:97; V:37. Fourth row, electronic pacemaker on "A-V dissociation." A:97; V:110.

lymphadenopathy and an osteolytic lesion of a rib that some form of neoplasm was suspected.

The failure to detect the tumor at the time of the initial thoracotomy was due to the small incision used for electrode implantation and the relative lack of right ventricular involvement. During the subsequent thoracotomies the previous fibrous reaction coupled with obliteration of the pericardial space by the tumor made identification impossible.

In Figure 7, the pacemaker artifact can be seen to precede each QRS complex. An interesting

TABLE I PREVIOUSLY REPORTED CASES OF RHABDOMYOSARCOMA OF THE HEART

Date	Author	Sex and Age (yr.)	Site of Origin	Metastatic Sites	Pericardium and Remarks
1909	Eschar [10] (Case IV) F,72		Right atrium and atrial septum	Adrenals	
1928	Bradley, Maxwell [11]	M,62	Myocardium (origin un- determined)	Kidney, liver, lungs	Invaded
1930	Leriche, Bauer [12]	F,53	Right atrium	Right hilus	Invaded
1932 1934	Muller [13]* Barnes, Beaver, Snell [14]	?,? F,62	Left atrium Right atrium, all of sep- tum	Lung, intestine, pancreas Pericardium, liver, lung	Obliterated (A-V block)
1936		F,16	Both atria	0	Hemopericardium, ruptured heart
1938	Larson, Sheppard [16]*	F,37	Left atrium	Kidney	
1940	Larson, Lidbeck [17]	M,75	Right ventricle	0	77
1942		M,39	Left ventricle	Liver, kidney, pancreas, intestine, brain, parotid	Hemopericardium
1947		M,14	Left ventricle	0	***
1947	Wells, Rowe, Joffe [20]	M,15	Right atrium, septum, right ventricle		
1950	Dubois, Baker, Soyster [21]	M,25	Right atrium	***	Hemopericardium (superior vena caval syndrome)
1950	Hargrove, Hall, Dienst [22]	M,43	Right atrium, right ven- tricle, tricuspid valve	Pleura, lung	Invaded
1953		M,40	Left atrium, right ven- tricle	Lung, thoracic lymph	Invaded
1953 1953	Kahrs [24] Longino, Meeker [25]	F,80 M,3 mo.	Right ventricle Epicardium	Lungs, rib Lungs, pleura, dia- phragm	Hemopericardium Invaded (superior vena caval syn- drome)
1953	Westad [26]	M,50	Right atrium and right ventricle	Left ventricle, pleura, mediastinum, thoracic lymph nodes	
1955	Engle, Glenn [27]	M,4 mo.	Right ventricle, left ven- tricle	Mediastinum, lungs, pulmonary artery, thymus	Hemopericardium
1955	Stoll, Lauer [28]	M,64	Right atrium	Lung, lymph nodes, epi- cardium	Invaded, hemoperi- cardium
1956	Manson, Rindskopf [29]	F,12	Atria, right ventricle	Pleura, lungs, breast, adrenals, mesenteric, thyroid, omentum, lymph nodes, bone, uterus	Effusion
1955	Malecka-Dymnicka, Zawrockawrzolek [30]	F,38	Left atrium	Pulmonary vein invasion	***
1956	Sta. Cruz, Sta. Ana [32]	M,8	Left atrium and atrial septum		
1957	Pascuzzi, Parkin, Brewer, Edwards [31]	F,25	Left atrium, atrial sep- tum	Jejunum, right ovary, hilar region, epicar- dium	Pulmonary osteo- arthropathy, he- mopericardium
1957	Bogdanovitch,	F,45	Right ventricle and left	Peritracheal lymph nodes	
1957	Idanov [33] (Case 1) Bogdanovitch,	F,65	pulmonary artery Right ventricle and in-	Lungs, brain, liver	
1057	Idanov [33] (Case II)	M,24	traventricular septum Right atrium	Lungs, liver	Effusion
1957 1958	Faber [34] Mannix, Lukash [36]	F,44	Pulmonary valve	Hilar region	Effusion
1958	Moiragni [35]	M,79	Right atrium and right ventricle		Hemopericardium
1959	Popov, Ivanov [37]	M,64	Pericardium	Myocardium, medias- tinum, liver, kidney	Invasion
1960	Dunnet, Symons, Stephenson [38]	F,60	Left atrium	Liver, ileum, brain, bone marrow	Mitral valve obstruction

^{*} Diagnosis questioned [46].

observation was the ability of the sarcomatous tissue to conduct an electrical impulse.

Pathologically, the extensive metastasis of the tumor is similar to that reported by Manson and Rindskopf [29]. However, metastasis of a rhabdomyosarcoma of the heart to the stomach was not noted in the previously reported cases. (Table 1.) Obliteration of the pericardial space both by postsurgical fibrosis and tumor invasion probably accounts for the lack of any pericardial fluid at postmortem examination. The absence of signs referable to the marked narrowing of the superior vena cava (Fig. 2) is unexplained. As can be noted in Table 1, atrial origin of a primary rhabdomyosarcoma is frequent.

The electrical apparatus presented in Figure 1 was the culmination of our experience with this patient. A detailed description of the transistorized pacemaker has been published elsewhere [3]. The first set of electrodes used consisted of single core stainless steel wire insulated with Teflon.® These wires were chosen because of previous experience with them during the immediate postoperative phase of open heart surgery. Because of the difficulty in maintaining prolonged myocardial fixation of these wires, a different type was obtained. These were composed of braided tantalum coated with Teflon, with swedged-on needles for ease of implantation. Although such wires offered greater flexibility and are technically more convenient to implant, they soon broke at the point of entry into the heart. Because of this complication a loop of wire was left between the pericardium and thoracic wall when the Roth electrode was implanted. This was done to prevent any excess wire tension which might develop because of the constantly changing heart position. The selection of the Roth electrode* was based on features which we believe to be important. Implantation is both easy and assured, although a somewhat larger surgical exposure is needed. In addition to flexibility, the wires of the Roth electrode are reinforced as they emerge from the electrode spikes. The only modification which we might suggest would be the use of a spiralled, flat stainless steel wire (tinsel wire) as used by Greer [45]. For long-term implantation, this wire has the advantages of great strength and flexibility. The plastic junction box was the innovation of the medical school instrument shop, † As can be seen, this box

† Courtesy of Mr. John Dahnke.

allows for the addition of a new electrical source without interrupting the circuit. In addition, another set of electrode wires can be attached without disturbing the first.

During times of surgery an intravenous drip of Isuprel in 5 per cent dextrose and distilled water provided satisfactory safeguard against

symptomatic bradycardia.

From our experience the pacemaker apparatus described in this communication is practical in the management of symptomatic forms of complete heart block. It is of interest that as the patient gained familiarity with and confidence in the pacemaker he was able to make heart rate adjustments which were physiologic for his particular activity. Patient rehabilitation can be undertaken since the threat of "Stokes-Adams" attack is removed.

SUMMARY

A forty-one year old man with obscure heart disease complicated by complete heart block is described. Eventually the patient died and a primary rhabdomyosarcoma of the atria with extensive metastasis was found. During the four and a half months which preceded his death the complete heart block was satisfactorily treated by use of a transistor pacemaker with indwelling myocardial electrodes. A description of the pacemaker apparatus used and the various features of its application are discussed.

A review of the previously reported cases of rhabdomyosarcoma of the heart is included.

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Serum Lipid Studies in Familial Hypercholesterolemic Xanthomatosis*

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Many clinical, epidemiologic and experimental studies suggest a relationship between serum lipid levels and the development of atherosclerosis. Although the many factors involved in this association are incompletely understood, some investigators believe that therapy directed toward correcting serum lipid elevations is justified in certain "high risk" groups. One such group includes subjects with familial hypercholesterolemic xanthomatosis which is characterized by a high incidence of premature and severe atherosclerosis.

An abundance of information is available concerning the influence of dietary alterations and drug therapy on serum lipid levels in normal subjects and in subjects with hypercholesterolemia of unknown etiology. However, relatively little information is available concerning the response of serum lipids to therapy in persons with familial hypercholesterolemic xanthomatosis. We recently studied such a patient in some detail. The effects of dietary fat alterations and of a cholesterol synthesis inhibitor on serum lipids in this patient will be presented.

CASE REPORT

A thirty year old white man was first seen by us in August 1959 for evaluation of a "high serum cholesterol." This abnormality was discovered in January 1959 during a family survey. He had been entirely asymptomatic. He specifically denied having had dyspnea, orthopnea, palpitation, chest pain, peripheral edema, hypertension, obesity and known heart or peripheral vascular disease. No gastrointestinal or genitourinary tract symptoms were noted. His past history revealed a mild attack of scarlet fever without complications, in addition to the usual childhood diseases. He had been quite active, participating without difficulty in numerous high school and army athletic

programs. A dietary history suggested well balanced meals, rich in dairy products. A moderate ethanol intake and smoking in excess of one pack of cigarettes daily were noted. The pertinent family history is shown in Figure 1. Note that five of twelve siblings have experienced cardiovascular symptoms before reaching the age of thirty-five years. In addition, hypercholesterolemia has developed in three others.

Physical examination revealed a well developed white man, 5 feet, 9 inches tall, and weighing 160 pounds. His blood pressure was 128/82 mm. Hg. No evidence of cardiovascular disease was found. Irregular nodular thickenings were apparent on both Achilles tendons and on several of the extensor tendons of both hands at the metacarpophalangeal joints. (Fig. 2.) According to the patient these lesions had been present for several years. They undoubtedly represent xanthoma tendinosum; however, no other xanthomatous lesions were found. The remainder of the physical examination was within normal limits.

Laboratory data included a normal hemogram, urinalysis, serologic tests for syphilis, blood urea nitrogen, creatinine and protein-bound iodine. Urea clearance was normal, and 38 per cent of the injected phenolsulfonphthalein was excreted in fifteen minutes. Serum total bilirubin was 0.3 mg./100 ml., 0.1 mg. of which was direct reacting; the result of the cephalin flocculation test was negative at forty-eight hours; thymol turbidity, 6 units; and serum alkaline phosphatase, 3.2 Shinowara, Jones and Reinhardt units. The serum total protein was 7.6 gm./100 ml. with an albumin fraction of 4.2 gm./100 ml.; and forty-five minute bromsulfalein retention was 4.5 per cent. The serum amylase was 72 Somogyi units/100 ml., and serum lipase, 1.3 Cherry-Crandall units. Total lipids in a seventy-two hour stool specimen were normal. Blood sugar concentrations, following the ingestion of 100 gm. of glucose, were as follows: fasting, 103 mg./ 100 ml.; half hour, 110 mg./100 ml.; one hour, 114 mg./100 ml.; one and a half hours, 129 mg./100 ml.; two hours, 110 mg./100 ml.; three hours, 97 mg./100 ml.; four hours, 94 mg./100 ml.; and

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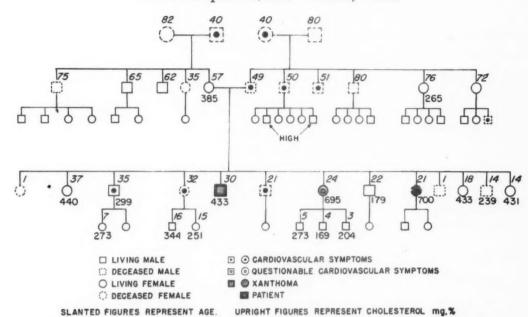


Fig. 1. Family pedigree. The patient is shown in the center; age thirty, serum total cholesterol of 433 mg./100 ml.

six hours, 107 mg./100 ml. Blood sugar concentrations, following intravenous glucose administration, were fasting, 97 mg./100 ml.; half hour, 139 mg./100 ml.; one hour, 97 mg./100 ml.; two hours, 93 mg./100 ml.; and three hours, 100 mg./100 ml. There was no sugar in the urine.

Several electrocardiograms, including a Master two-step test, were within normal limits. A chest roentgenogram and intravenous pyelogram were within normal limits.

Serum total cholesterol concentrations were reported to have varied from 398 to 536 mg./100 ml. prior to participation in this study. The patient re-

mained ambulatory and asymptomatic throughout his hospitalization.

METHODS AND MATERIALS

Diets. The patient consented to a variety of studies designed to find the best practical means of lowering his serum cholesterol. Basically, four diets were used in this study (Table 1) in addition to a therapeutic trial of MER/29® (triparanol). The control diet was designed as an idealized menu for his weight and physical activity, and was composed of foods similar to his usual food choices. The low fat diet was constructed to keep the total calorie and protein content similar to the control menu while substituting carbohydrate isocalorically for as much of the

TABLE I COMPOSITION OF DIETS

	Diet									
Composition	Con- trol	Low Fat	Corn Oil No. 1	Corn Oil No. 2						
Total calories/day	2,470	2,140	2,290	2,475						
Protein (gm./day)	99	84	89	91						
Carbohydrate (gm./day).	291	408	257	290						
Total fat (gm./day) Corn oil supplement	110	22	105	117						
(gm./day)			42	90						
% Calories as fat	41	9	41	43						



Fig. 2. Xanthoma tendinosum. Note the irregular nodular thickenings apparent on the index, third and fourth fingers at the metacarpophalangeal joints. These lesions are firmly attached to the extensor tendons.

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Table II SAMPLE MENU FOR THE SECOND CORN OIL DIET (2,475 CALORIES)*

Menu	gm.
Breakfast	
Orange juice	200
Egg (1 medium)	50
Cornflakes	25
Bread (1 slice)	25
Jelly	14
Sugar	12
Fresh skim milk	240
Non-fat milk solids	5
Corn oil	30
Lunch or dinner	
Lean meat (beef or veal)	60
Potato	100
Vegetable (low carbohydrate)	100
Bread (1 slice)	25
Jelly	14
Fruit (about 150 calories)	
Salad (raw vegetables)	as desired
Gravy (skim milk and flour)	80
Chili sauce or ketchup	10
Fresh skim milk	240
Non-fat milk solids	5
Corn oil	30

^{*} All foods are cooked without additional fat.

fat as possible, utilizing "ordinary foods." Only 5 ounces of lean meat were allowed daily and this accounted for the entire fat content of 22 gm. The first corn oil diet was an isocaloric substitution of 42 gm. of corn oil for fat in the control diet. Seven ounces of lean meat were allowed in the daily ration. In the second corn oil diet 90 gm. of corn oil was substituted for fat in the control period. A sample menu is shown in Table II. MER/29 was tested by giving one 250 mg. capsule daily for a three week period while the patient was adhering to the control diet.

The temporal sequence of these therapeutic trials was as follows: period I, control diet, fourteen days; period II, low fat diet, nineteen days; period IIIa, corn oil diet No. 1, nineteen days; three month interim period on corn oil diet no. 1 (not hospitalized); period IIIb, corn oil diet no. 1, seven days; period IV, control diet, twenty-one days; period VI, control diet, twenty-one days; period VI, control diet, twenty-one days; period VII, control diet plus MER/29, twenty-one days; period VIII, control diet, five days.

Except for the three month interim period all diets were weighed and served at a special diet table. On several occasions small portions of unpalatable vegetables, bread and meat were left at the table while the patient was ingesting the low fat and first corn oil

diets. This food was "weighed back" and considered in the diet calculations. Thus the figures in Table 1 indicate the average composition of food ingested. Corn oil, served as Mazola Oil, was consumed as such with each meal. During the study physical activity was kept relatively constant. Body weight remained stable at 160 ± 2 pounds.

Lipid Analyses. All lipid analyses were performed in duplicate. Venous blood was drawn three times weekly at two or three day intervals. Serum was separated from whole blood and committed to the appropriate extraction. Serum total cholesterol and cholesterol esters were determined by the method of Schoenheimer and Sperry [1]. The method of Fiske and Subbarow [2] was used to measure lipid phosphorus. Total lipids were estimated by the colorimetric method described by Bragdon [3]. Non-esterified fatty acids (NEFA) were determined by the method of Dole [4]. Tri-, di- and monoglycerides were separated on small silicic acid columns and measured by a colorimetric method [5].

RESULTS

Because of the considerable variation of serum lipid concentrations within each period, mean values are assembled in Table III and graphed in Figures 4 and 5. Only the six samples collected during the last two weeks of each period are used in order to minimize the possible carry-over effects from previous periods. The probability of differences between mean values being significant is shown in Table IV. Probabilities not reaching the 5 per cent level are noted as non-significant (n.s.).

Cholesterol. All serum total and free cholesterol concentrations obtained during the study are plotted in Figure 3; the values obtained in each period are connected. Note that the changes in free cholesterol seem to parallel those of total cholesterol.

The diets in control periods I, IV and VI were identical. Mean total cholesterol values were similar in periods IV and VI; however, these were significantly higher than the mean in period I. (Fig. 4, Tables III and IV.) The mean values were similar in periods II (low fat diet), IIIa (corn oil diet no. 1), and V (corn oil diet no. 2). These values were significantly lower than those of control periods IV and VI, but higher than period I. The mean serum cholesterol concentration in period VII (MER/29) was significantly lower than in control period VI but did not attain the low levels observed during the low fat or corn oil diets.

During the first week on the low fat diet there was a definite upward trend in serum total cho-

TABLE III SERUM LIPID VALUES

Means and Standard Deviations for the Six Samples Collected During the Last Two Weeks of Each Period

Period	Diet	Total Cholesterol (mg./100 ml.)	Free Cholesterol (mg./100 ml.)	Lipid Phosphorus (mg./100 ml.)	Triglycerides (mg./100 ml.)	Diglycerides (mg./100 ml.)	Mono- glycerides (mg./100 ml.)	Non- Esterified Fatty Acids (mEq./L.)	Total Lipids (mg./100 ml.)
1	Control	312 ± 30	95 ± 7	15.7 ± 1.1	119 ± 21	9.9 ± 3.0	1.8 ± 1.6	467 ± 144	1,025 ± 11
33	Low fat	379 ± 19	110 ± 8	14.3 ± 1.2	116 ± 17	13.7 ± 3.2	8.7 ± 4.7	686 ± 116	887 ± 81
ша	Corn oil No. 1	373 ± 19	94 ± 21	13.2 ± 0.9	121 ± 20	15.5 ± 8.3	3.5 ± 3.3	316 ± 115	958 ± 64
IV	Control	447 ± 22	129 ± 6	13.1 ± 1.5	101 ± 5	13.8 ± 2.0	4.0 ± 2.1	595 ± 48	982 ± 55
v	Corn oil No. 2	367 ± 53	100 ± 20	11.2 ± 1.8	100 ± 16	11.8 ± 1.2	1.4 ± 1.0	293 ± 172	917 ± 56
VI	Control	435 ± 38	118 ± 9	15.2 ± 1.7	119 ± 13	13.9 ± 1.5	3.5 ± 1.0	622 ± 304	989 ± 68
VII	Control and MER/29	398 ± 10	111 ± 7	14.6 ± 0.4	103 ± 27	9.9 ± 4.5	2.3 ± 1.5	501 ± 133	936 ± 37

TABLE IV

COMPARISON OF MEAN SERUM LIPID VALUES
The Probability of Differences Between Periods Being Significant

		Total	Free	Lipid	(Glycerides	Non- Esterified		
Period	s Compared	Choles- terol	Choles- terol	Phos- phorus	Tri	Di	Mono	Fatty Acids (NEFA)	Total Lipids
I	and IV	P < 0.001	P < 0.001	P < 0.010	n.s.	P < 0.025	n.s.	n.s.	n.s.
I	and vi	P < 0.001	P < 0.001	n.s.	n.s.	P < 0.025	n.s.	n.s.	n.s.
IV	and vi	n.s.	P < 0.025	P < 0.050	P < 0.010	n.s.	n.s.	n.s.	n.s.
I	and 11	P < 0.001	P < 0.005	n.s.	n.s.	n.s.	P < 0.010	P < 0.025	P < 0.00
I	and ma	P < 0.005	n.s.	P < 0.005	n.s.	n.s.	n.s.	n.s.	P < 0.050
II	and ma	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	P < 0.001	n.s.
II	and IV	P < 0.001	P < 0.001	n.s.	P < 0.050	n.s.	n.s.	n.s.	P < 0.005
ma	and iv	P < 0.001	P < 0.005	n.s.	n.s.	n.s.	n.s.	P < 0.001	n.s.
шa	and v	n.s.	n.s.	P < 0.050	n.s.	n.s.	n.s.	n.s.	n.s.
IV	and v	P < 0.010	P < 0.010	n.s.	n.s.	n.s.	P < 0.025	P < 0.005	n.s.
VI	and vii	P < 0.050	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.

Note: n.s. = not significant at the 5 per cent level.

lesterol (Fig. 3), an increase of approximately 90 mg./100 ml. The values then leveled off near the mean obtained in period II. A more striking downward trend was seen in period v (corn oil diet no. 2), continuing through the entire three weeks of observation (a fall of approximately 125 mg./100 ml.). A prompt recovery toward control values was seen in period vI. Note also that the highest serum total cholesterol concentration obtained in this study was observed while the patient was still on the control diet five days after MER/29 therapy was discontinued (547 mg./100 ml.).

Lipid Phosphorus. Mean lipid phosphorus concentrations were similar in control periods 1 and VI; however, these were significantly higher than the mean for control period IV. (Fig. 4, Tables III and IV.) The mean value for period IIIa (corn oil diet no. 1) was significantly lower than that for period I, and the mean in period V (corn oil diet no. 2) was lower than that in period IIIa. In the control period, following the second corn oil diet, lipid phosphorus values rose and did not fall significantly with MER/29. The mean in period II (low fat diet) was between the first control and first corn oil diet means.

Glycerides. The mean triglyceride value was significantly higher in control period vI than in control period IV, but was similar to the mean in period I. (Fig. 5, Tables III and IV.) During the

Serum Lipid Studies-Powell, Vacca

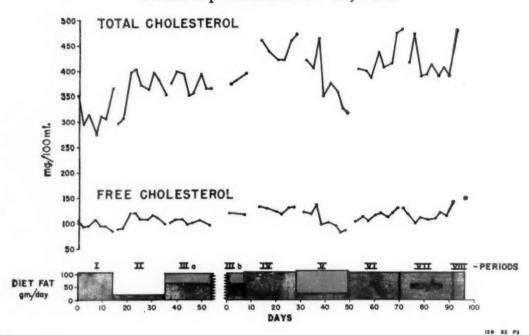


Fig. 3. Serum total and free cholesterol concentrations. All values obtained during the study are plotted, and those within each period are connected. The fat intake in each period is shown. Slanted lines indicate the amount of corn oil added. There was a three-month interim between periods IIIa and IIIb.

low fat diet (period II), triglycerides were significantly higher than in period IV, but were similar to those of period I. The mean diglyceride concentration in control period I differed significantly from control periods IV and VI. Mean monoglyceride values were not significantly different for the three control periods. An increase occurred, however, during the low fat diet when compared to control period I, and a decrease occurred in period V (corn oil diet no. 2) when compared to control period IV.

It is interesting to note that during the first week on the low fat diet, tri, di and monoglycerides increased a sum total of approximately 40 to 45 mg./100 ml. and then fell during the last two weeks of this period.

Non-esterified Fatty Acids (NEFA). Mean NEFA values were not significantly different in control periods I, IV and VI. (Fig. 5, Tables III and IV.) Rather large and significant decreases occurred during both corn oil diets (periods IIIa and V) when compared to period II (low fat diet) or to control period IV, respectively. The addition of MER/29 did not significantly lower NEFA values from the preceding control period VI.

Total Lipids. Mean values for the serum total lipid determinations were not significantly

different when control periods were compared. (Fig. 4, Tables III and IV.) The mean value in period II (low fat diet) was significantly lower than those of control periods I and IV. The values obtained for both corn oil periods and MER/29 were between the control and low fat means.

COMMENTS

The diagnosis of familial hypercholesterolemic xanthomatosis seems well established in this patient. Persistently elevated serum cholesterol concentrations, with slight elevation in total lipids, slight elevation in lipid phosphorus and normal neutral fat values, are expected in this syndrome. The serum was translucent. Although the tendon lesions were not biopsied, they were typical of xanthoma tendinosum; and similar lesions in a sister were proved microscopically. The causes of secondary hypercholesterolemia seem adequately excluded. Although the patient remains asymptomatic at this time, a glance at the family pedigree (Fig. 1) reveals unmistakable evidence of premature and severe atherosclerotic complications. Nine of thirteen siblings have premature arteriosclerotic heart disease and/or high serum cholesterols. Furthermore, two others died in infancy and

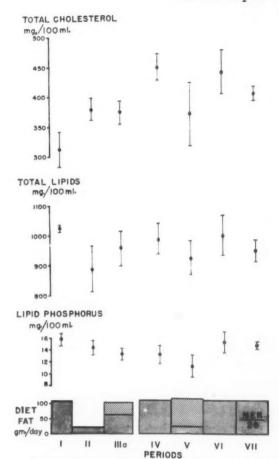


Fig. 4. Serum lipid values: means and standard deviations for the six samples collected during the last two weeks of each period. The fat intake in each period is shown. Slanted lines indicate the amount of corn oil added. There was a three-month interim between periods III and IV.

cannot be properly evaluated. This patient then certainly belongs in the so-called "high risk" group.

In general, therapeutic trials in this patient have been discouraging. There was no regression in the size of the tendon xanthoma. Even the most marked fall in serum cholesterol, of 125 mg./100 ml. during the second corn oil diet period, represents a decrease of only 28 per cent, and normal cholesterol values were never approached. We nevertheless present this case report for two reasons: first, because of the opportunity for comparing several therapeutic trials in the same patient while under rigid dietary control; and second, to report our data on several serum lipid fractions, including newer methodology for glyceride determinations. We have compared the effects of several diets and MER/29 therapy on serum lipids in this patient.

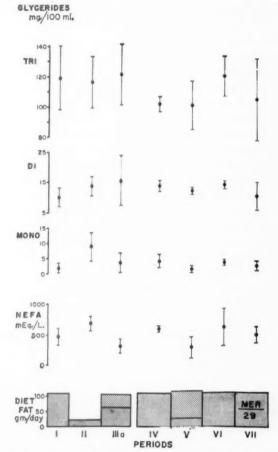


Fig. 5. Serum lipid values: means and standard deviations for the six samples collected during the last two weeks of each period. Triglycerides, diglycerides, monoglycerides and non-esterified fatty acids are plotted. The fat intake in each period is shown. Slanted lines indicate the amount of corn oil added. There was a three-month interim between periods IIIa and IV.

Because three week trial periods were used, long-term effects are unknown. Only in the second corn oil diet period, however, was a continuing downward trend noted during the last week. (Fig. 3.) This downward trend was observed for serum total cholesterol, free cholesterol and lipid phosphorus.

All meals were prepared in a hospital kitchen and served at a special diet table. Caloric intake throughout the study proved adequate to maintain weight. The low fat diet was originally designed as an isocaloric substitution of carbohydrate for as much of the control diet fat as possible. This 20 gm. fat diet, however, was unpalatable. As a result, small portions of bread, vegetables and meat were left on several occasions, which accounts for the lower caloric and protein content of this diet. The average

composition of food consumed is shown in Table 1. The first corn oil diet, on the other hand, was tolerated quite well although some food was left at the table during this period. Note that approximately 60 gm. of dietary fat were allowed. The second corn oil diet (25 gm. of dietary fat) was just as unpalatable as the low fat diet; however, all food was consumed. While this dietary control will not compare with formula diets, it is more rigid than many studies reported in which patients were followed up on an outpatient basis. We hope that the use of menus prepared in this fashion will have some practical application. Certainly with suitable patient cooperation these diets could be followed and prepared in the home, using ordinary foods. Note the sample menu for the second corn oil diet. (Table 11.) Corn oil was served in several ways; but our patient preferred to take 1 ounce as such with each meal rather than to disguise it with food or beverages.

Among the more significant differences in mean total cholesterol concentrations we observed were those between control period 1 and control periods IV and VI. Diets, body weight, activity, and all other factors, as far as we can determine, were identical in all three periods. Still, mean differences of 120 to 135 mg./100 ml. were observed. Others have noted wide fluctuations in serum cholesterol [6-10]. The significance of this variation, even when the diet is rigidly controlled, seems obvious. As pointed out by Wilkinson and his associates [6], these fluctuations present a hazard in the interpretation of studies dealing with cholesterol lowering agents. The variation in mean cholesterol concentrations between control periods makes interpretation of our data quite difficult. For example, when compared with control periods IV or vi, our patient had significant decreases in total cholesterol concentrations on the low fat diet, both corn oil diets, and to a lesser extent while on MER/29 therapy. By contrast, all these therapeutic efforts resulted in increased concentrations if compared to the first control period.

The serum cholesterol lowering effect of dietary fat alterations in subjects with familial hypercholesterolemic xanthomatosis has been described previously. Urbach et al. [11] found low fat diets (20 gm.) caused a lowering of serum cholesterol in nine patients observed for several years. The response was noted to be less striking, however, in patients with tendon

xanthoma. Malmros and Wigand [12] were of the opinion that a reduction in dietary fat was of little value unless the diet was completely fat free. More recently, the substitution of unsaturated oils for animal fat in the diet has been described, and the results of many investigators have confirmed this therapeutic approach [13–16]. Others have tried estrogens [17,18], sitosterol [6,12,17,19], heparin [17,20] and nicotinic acid [17,21]. With all forms of therapy mentioned, however, results in familial hypercholesterolemic xanthomatosis have been somewhat less than impressive, with serum cholesterol changes of only about 20 to 40 per cent and rarely have normal values been achieved.

Recently a cholesterol synthesis inhibitor called MER/29 (triparanol) was marketed. Serum cholesterol levels are said to fall beginning in five to ten days and achieving a maximum effect after two to eight weeks [22]. Too few patients have been studied thus far with familial hypercholesterolemic xanthomatosis to permit an adequate evaluation. Several cases, however,

have been reported [23,24]. We believe that the comparison of different therapeutic approaches in this patient is of value. While there was no real difference in mean total cholesterol values noted for periods II, IIIa and v (the low fat and corn oil diets), the continuing downward trend during the second corn oil diet period, with a prompt rise in control period vi, was the most significant change noted in this study. (Fig. 3.) Because the serum cholesterol values were still falling when the diet was changed, even lower levels might have been obtained if the corn oil diet had been continued. That unsaturated oils added to a low fat diet will cause further lowering of serum cholesterol has been observed in normal subjects [25] and in several patients with hypercholesterolemia [16,26].

Even less information is available concerning the response of other serum lipids in patients with familial hypercholesterolemia to various therapeutic manipulations. In our patient the serum lipid phosphorus reached its lowest levels on the corn oil diets; and a significant fall was not achieved with the low fat diet or MER/29 therapy. (Fig. 4, Table III.) The lowered lipid phosphorus concentrations achieved with unsaturated oils support the findings of others [14,16,27]. Non-esterified fatty acid values were significantly lowered in the corn oil diet periods; however, no significant changes were observed

with the low fat diet or MER/29. (Fig. 5, Table III.) We are not aware of other published data on NEFA values with which to compare these results.

Tri-, di- and monoglycerides were measured directly. They were not significantly lowered by the low fat diet, the corn oil diets, or MER/29. (Fig. 5, Table III.) Furthermore, while there was a moderate increase of glycerides during the first week of the low fat diet, these values fell toward the baseline later in the period. This rise in glycerides did not approach the marked elevations noted by Ahrens et al. [14,28] in several patients when carbohydrate was substituted isocalorically for fat. Triglyceride values in these patients, however, were determined indirectly and this may account for part of the difference. Measurements of serum glycerides or "neutral fat" in many previous studies have been values derived by subtracting cholesterol and phospholipid values from a total lipid estimation. Thus potential errors in methodology may be increased, and factors are used which are only approximations. In this study the direct method yielded lower triglyceride values. For example, if one summates the mean cholesterol, phospholipid, glyceride and NEFA centrations for each study period, these "total lipid" measurements range from 40 to 190 mg./ 100 ml. less than the colorimetric oxidative method used in total lipid measurements. One exception is noted; the values correspond closely in period II. If, then, neutral fat had been determined indirectly in this study, the resulting triglyceride values would have been proportionately higher.

The data presented in this report indicate that our patient was relatively resistant to all therapeutic trials. Our results, however, are comparable to those reported by others. The data have been difficult to interpret because of the variation noted when comparing control periods. It is our belief, nevertheless, that for this patient, the second corn oil diet yielded the best lowering effect for the serum lipids measured. If MER/29 had been given for longer than three weeks, a more striking effect might have been achieved. The last week in this period, however, did not show a continuing downward trend.

While the conclusions derived from study of a single patient must be limited, we hope that these data, when added to and compared with the results of other investigators, will help toward a better understanding of the proper thera-

peutic approach to familial hypercholesterolemic xanthomatosis.

SUMMARY

The effects of dietary fat alterations and of MER/29 therapy on serum lipids in a patient with familial hypercholesterolemic xanthomatosis are presented. The diets used in this study include a control diet, a 20 gm. fat diet in which carbohydrate was substituted isocalorically for fat in the control period, a diet in which 40 gm. of corn oil was substituted isocalorically for fat in the control period, and a diet in which 90 gm. of corn oil was substituted isocalorically for fat in the control diet.

Serum total cholesterol, free cholesterol, lipid phosphorus, tri-, di- and monoglycerides, non-esterified fatty acids, and total lipids were determined three times weekly throughout the study.

The results are difficult to interpret because of the variation in serum lipid concentrations between control periods. However, it is believed that the best response was achieved with the second corn oil diet when the serum total cholesterol values decreased approximately 125 mg./100 ml., a fall of 28 per cent. Lipid phosphorus and NEFA mean concentrations also decreased on this corn oil diet. A less impressive fall in serum total cholesterol was observed with MER/29, and no significant change in lipid phosphorus was noted. These data are discussed and compared with the results of others.

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the first comprehensive regulator of female cyclic function

ENOVID®

THE BASIC ACTION

Enovid closely mimics the balanced progestational-estrogenic action of the functioning corpus luteum. This action is readily understood by a simple comparison. In effect, Enovid induces a physiologic state which simulates early pregnancy—except that there is no placenta or fetus. Thus, as in pregnancy, the production or release of pituitary gonadotropin is inhibited and ovulation suspended; a pseudodecidual endometrium ("pseudo" because neither placenta nor fetus is present) is induced and maintained.

Further, during Enovid therapy, certain symptoms typical of normal pregnancy may be noted in some patients, such as nausea—which is usually mild and disappears spontaneously within a few days—breast engorgement, some degree of fluid retention, and often a marked sense of wellbeing. There is no androgenicity. Enovid is as safe as the normal state of pregnancy.

THE BASIC APPLICATIONS

- 1. Correction of menstrual dysfunction. Emergency treatment of severe dysfunctional uterine bleeding is promptly effective following the administration of Enovid in larger doses. Cyclic therapy with Enovid controls less severe dysfunctional uterine bleeding. In amenorrhea cyclic therapy with Enovid establishes a pseudodecidual endometrium providing the patient has endometrial tissue capable of response.
- 2. Ovulation suppression (to suspend fertility). For this purpose Enovid is administered cyclically, beginning on day 5 through day 24 (20 daily doses). The ovary remains in a state of physiologic rest and there is no impairment of subsequent fertility. When Enovid is prescribed for this cyclic use over prolonged periods, a total of twenty-four months should not be exceeded until continuing studies indicate that its present lack of undesired actions continues for even longer intervals. Such studies are now in their seventh year and will regularly be reviewed for extension of the present recommendation.



...unfettered

- 3. Adjustment of the menses for reasons of health (impending hospitalization for surgery, during treatment of Bartholin's gland cysts, acute urethritis, rectal abscess, trichomonal or monilial vaginitis), or other special circumstances considered valid in the opinion of the physician. For this purpose Enovid may be started at any time in the cycle up to one week before expected menstruation. Upon discontinuation, normal cyclic bleeding occurs in three to five days.
- 4. Endometriosis. Continuous therapy with ENOVID corrects endometriosis by producing a pseudodecidual reaction with subsequent absorption of aberrant endometrial tissue.
- 5. Threatened and habitual abortion. Enough should be used as emergency treatment in threatened abortion although symptoms may occur too late to be reversible. Continuous therapy with Enough in habitual abortion is based on the physiology of pregnancy. Enough provides balanced hormone support of the endometrium, permitting continuation of pregnancy when endogenous support is otherwise inadequate.
- 6. Endocrine infertility. ENOVID has been used successfully in *cyclic* therapy of endocrine infertility, promoting subsequent pregnancy through a probable "rebound" phenomenon.

THE BASIC DOSAGE

Basic dosage of Enovid is 5 mg. daily in cyclic therapy, beginning on day 5 through day 24 (20 daily doses). Higher doses may be used with complete safety to prevent or control occasional "spotting" or breakthrough bleeding during Enovid therapy, or for rapid effect in the emergency treatment of dysfunctional uterine bleeding and threatened abortion.

ENOVID is available in tablets of 5 mg. and 10 mg. Literature and references, covering more than six years of intensive clinical study, available on request.

SEARLE

Research in the Service of Medicine

PERIPHERAL PHYSICIANS PRESCRIBE

more often than any other diuretic

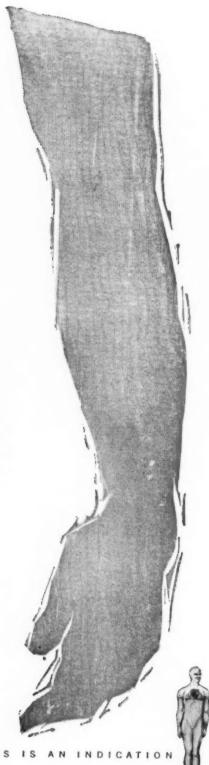
"This study concerned 56 patients with localized swelling in an upper or lower extremity occurring after thrombophlebitis, ulcer of the leg,...trauma, or fracture." "Conventional treatment appropriate for the specific condition was supplemented with diuretics and dietary salt limitation. Chlorothiazide (Diuril) in doses of 1 to 2 Gm. a day was used in all cases..." "All patients showed measurable decrease in their edema, and the response was good or excellent in all but six."

Bedell, W.C.: J.A.M.A. 173:1811, August 20, 1960. Supplied: 250-mg. and 500-mg. scored tablets DIURIL chlorothiazide in bottles of 100 and 1000.

Additional information is available to the physician on request. DIURIL is a trademark of Merck & Co., Inc.



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A MORE CLINICALLY USEFUL DIURETIC/ANTIHYPERTENSIVE

active antihypertensive broad benefit clinically confirmed convenient control dosage dexterity dependable diuresis enhanced effectiveness foremost flexibility increased individualization long lasting

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"enhanced effectiveness"_In a 24-hour dose response study, RENESE produced a greater increase in sodium excretion than has been shown with four other currently available thiazides. In a controlled study of patients with hypertensive cardiovascular disease, free of detectable edema, the 24-hour urinary volume increased by an average of 1.8 liters with an accompanying average weight reduction of 1.4 Kg. following a single 8 mg. dose of RENESE. The enhanced effectiveness of RENESE may produce response where previous therapy has failed or improve the response to present therapy.

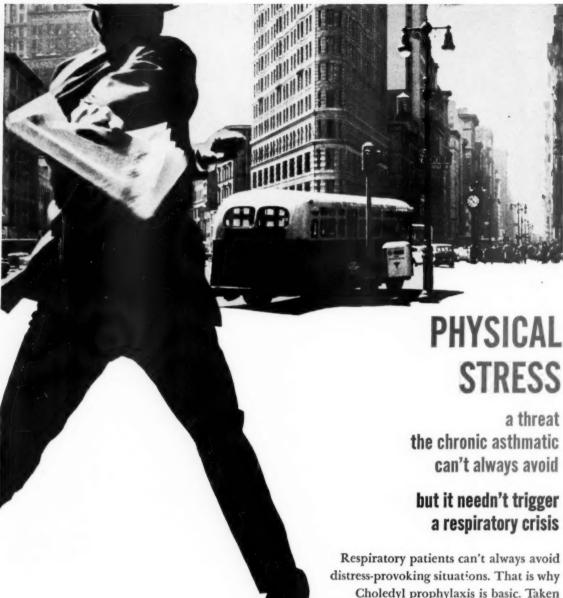
1. Ford, R. V.: Current Therap. Res. 3:320, July, 1961



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FOR PRODUCT INFORMATION TURN TO PAGE 23



Respiratory patients can't always avoid distress-provoking situations. That is why Choledyl prophylaxis is basic. Taken regularly-daily-Choledyl helps prevent severe respiratory flare-ups by affording sustained bronchodilatation. Throughout long-term use, Choledyl

is uniformly effective. And even in older patients, gastric upset and other unwanted effects are rare. Dosage: one 200 mg. tablet q.i.d.

Precautions: Side effects have been minimal but may include CNS stimulation or, rarely, palpitation. Full dosage information, available on request, should be consulted before initiating therapy.

to avoid the crisis in chronic bronchitis, chronic asthma, emphysema



brand of oxtriphylline

For the irritable G.I. tract

Milpath acts quickly to suppress hypermotility, hypersecretion, pain and spasm, and to allay anxiety and tension with minimal side effects.

AVAILABLE IN TWO POTENCIES

MILPATH-400-Yellow, scored tablets of 400 mg. Miltown (meprobamate) and 25 mg. tridihexethyl chloride.

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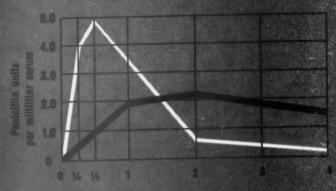


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A potent oral penicillin for high therapeutic efficacy

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Hours after administration

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Palatable, convenient, well tolerated

PEN. VEE K is palatable, convenient (tablet or liquid), and well tolerated. These factors encourage good patient cooperation, which helps prome rapid recovery.

References: 1. Peck, F.B., Jr., and Griffith, R.S.: Antibiotics Annual 1957-58, Medical Encyclopedia, Inc., p. 1004. 2. White, A.C., et al.: Antibiotics Annual 1955-56, Medical Encyclopedia, Inc., p. 496.

For further information on limitations, administration, and prescribing of PEN-VEE K, see descriptive literature or current Direction Circular.

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Cremomycin_® provides rapid relief of virtually all diarrheas

NEOMYCIN—actively bactericidal against a wide range of gram-negative intestinal pathogens, but relatively ineffective against certain diarrhea-causing organisms.

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to prevent pain and anxiety in angina

For your angina patients, EQUANITRATE helps control pain and anginatriggering anxiety. EQUANITRATE reduces the number and severity of attacks, increases exercise tolerance, and lessens nitroglycerine dependence. Russekt reports "The best results... in both clinical and electrocardiographic response, were observed with a combination of meprobamate and pentaerythritol tetranitrate [EQUANITRATE] in the patients studied."

For further information on the limitations, administration, and prescribing of EQUANITRATE, see descriptive literature or current direction circular.

†Russek, H.I.: Am J. Cardiol. 3:547 (April) 1959.

Supplied: EQUANITRATE 10 (200 mg. meprobamate, 10 mg. pentaerythritol tetranitrate), white oval tablets, vials of 50. EQUANITRATE 20 (200 mg. meprobamate, 20 mg. pentaerythritol tetranitrate), yellow oval tablets, vials of 50.

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Equanitrate

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Full thiazide therapy that goes easy on the potassium

"ONCE A DAY-EVERY DAY"

ENDURON

Methyclothiazide, Abbott

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Enduron gives you full measure of the familiar thiazide benefits: diuresis, sodium and chloride elimination, antihypertensive action. It is potent (peak dose is 10 mg., versus 2000 mg. for chlorothiazide, for example). One 10-mg. dose yields sodium excretion equal or superior to previously available thiazides in any size dose. Longacting, too: every tablet delivers 24 hours' continuous therapy, so that rarely does your patient require more than one daily dose.

Yet with all this efficacy, Enduron is surprisingly sparing of serum potassium. The *single* daily dose causes but a *single* temporary peak of potassium loss, compared with multiple peaks of multi doses. Moreover,

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Thus Enduron produces less potassium excretion per unit of sodium excreted, so that depletion rarely becomes a problem.

Use Enduron with patients who have mild to moderate hypertension, or patients with edema (as in congestive heart failure, the nephrotic syndrome, hepatic cirrhosis, premenstrual tension, or steroid therapy).

Observe its convenience and effectiveness. We predictyou'llbe glad you used it.







Hold down that soaring blood pressure with just one daily dose

NEW THIAZIDE RAUWOLFIA ANTIHYPERTENSIVE

ENDURONYL

(Methyclothiazide and Deserpidine, Abbott)—ENDURON™ and HARMONYL®

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Of course, Enduronyl can't cure your patients' hypertension...but it certainly can simplify treatment. It enables you to provide the fullest advantages of thiazide and rauwolfia—in a single convenient agent—and you'll need just one dose daily. Note these two components:

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How Supplied: Tablets of 500 mg, envelopes of 6 tablets, boxes of 5 and 25 envelopes; also bottles of 500.

1. Whitehouse, W. M.: Iopanoic acid. Ann. New York Acad. Sc. 78:809, July 2, 1959. Z. Baker, H. L., Jr., and Hodgson, J. R.: Further studies on the accuracy of oral cholecystography, Radiology 74:239, Feb. 1960.

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In over six years of clinical use...



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Effective

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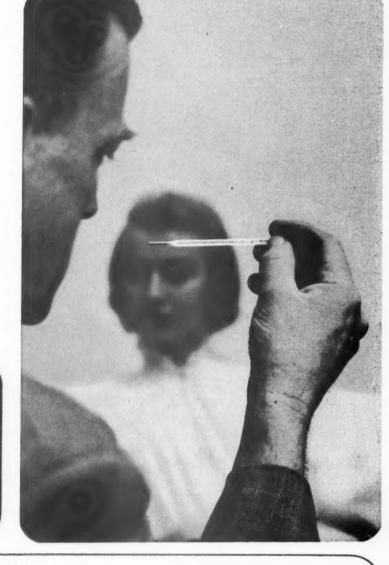
- 1 simple dosage schedule relieves anxiety dependably without altering sexual function
- 9 does not produce ataxia
- 3 no cumulative effects in long-term therapy
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 m \, does\ not\ produce\ Parkinson-like\ symptoms,}$ liver damage or agranulocytosis
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WHEN INFECTION CALLS FOR **PROLONGED PENICILLIN** ACTION

INJECTION

Benzathine Penicillin G, Wyeth

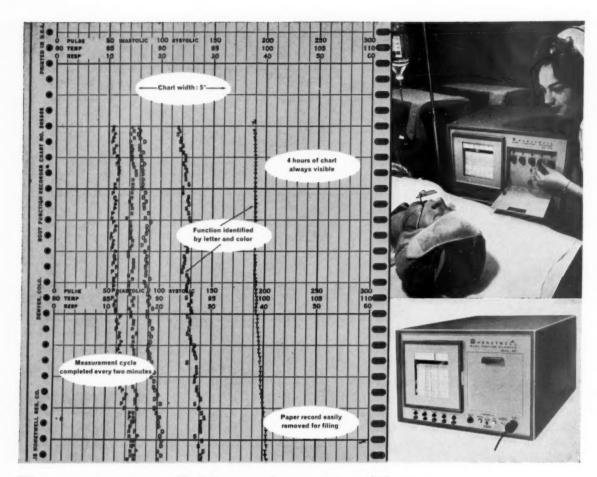
effective treatment of many upper respiratory infections

- produces blood levels lethal to most pathogens common in upper respiratory infections
- -streptococci, pneumococci, and penicillin-susceptible staphylococci produces prolonged blood levels, thus tending to prevent reinfection, relapse, or early recurrence
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Specifically designed to monitor the condition of critically-ill and post-operative patients, the Honeywell Body Function Recorder automatically measures and records changes in body temperature, pulse rate, respiration rate, systolic and diastolic blood pressure. Medical authorities familiar with the special requirements for intensive care agree that the relative behavior of these physiological functions provides an accurate picture of the patient's overall condition.

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Listica is not "just another tranquilizer." We, therefore, call it The First Selective Tensitropic. Here are the reasons why:

New Listica allays tension/anxiety in as many as 89% of cases by selectively inhibiting impulses through internuncial pathways of the central nervous system. However, it does not affect the unconditioned response; thus, Listica does not induce apathy or impair acuity.

The past three and one-half years of clinical studies have demonstrated the safety and efficacy of Listica in 1,759 patients. There have been no reports of contraindications, toxicity, habituation or serious side effects.

One tablet q.i.d. is adequate dosage to allay tension/anxiety, maintain acuity, and promote eunoia *—"a normal mental state." This simple, effective dose remains the same, even in maintenance therapy.

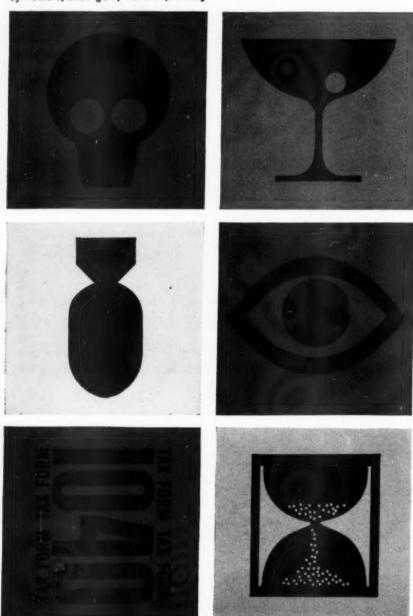
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maintains acuity...promotes eunoia*...
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lifts the facade of New Listica allays tension/anxiety in as many as 89% of cases, 2-13 by selectively TENSION/ANXIETY inhibiting impulses through internuncial pathways of the central nervous system. Whether the patient's tension/anxiety is psychosomatic or a complication of somatic disorder, Listica reduces or eliminates the excess impulsivity seen in tension /anxiety states.

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without known Listica is safe, as well as effective. Chronic studies14 in rats (12 months) and dogs toxicity or (6 months) were free of toxic manifestations at oral dosage levels as high as 200 contraindications mg./kg./day (approximately 10 times the recommended human dosage). No macroscopic or microscopic changes in tissues, organs or blood indicative of toxicity were observed, even at doses up to 320 mg./kg. In humans, there have been no adverse blood, urine or cardiac changes; liver profiles were negative, and jaundice has not been noted.

without serious During three and one-half years of clinical study in 1,759 patients, 2-13 Listica has side effects produced no serious side effects. Less than 4% of patients experienced any side or habituation effects, and these were invariably minor and transient. Most frequent (38 cases) was mild drowsiness, which disappeared after the first few days of Listica therapy. Habituation, cumulative effects, or withdrawal symptoms have not been noted, even in patients taking Listica as long as two years.

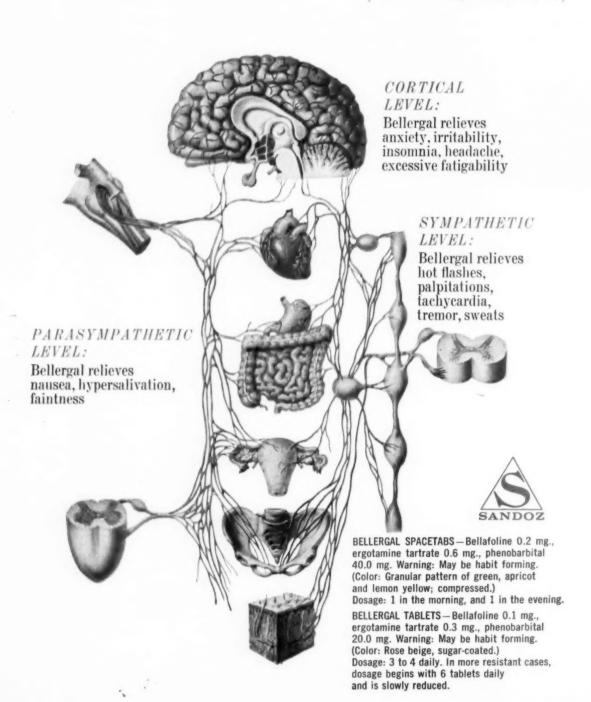
with convenient One Listica tablet, q.i.d., is the recommended dosage. Listica is supplied in bottles dosage and of 50 tablets on prescription only, by pharmacies everywhere. Each tablet contains availability 200 mg. of Hydroxyphenamate, Armour.

¹Bastian, J. W.: Classification of CNS Drugs by a Mouse Screening Battery. To be published in Intern. Arche, de Pharmacodynamie; ²Hubata, J. A., and Hecht, R. A.: Review of Clinical Use of Hydroxyphenamate (Listica) in 1,759 Patients. To be published in Clinical Medicine; ³Taub, S. J.: Management of Anxiety in Allergic Disorders—New Approach. To be published in Psychosomatics; ⁴Cahn, B.: Experience with a New Tranquilizing Agent (Hydroxyphenamate). *Ibid*; ⁵Davis, O.F.: On Use of Hydroxyphenamate in the Alexandra Listical Agents and Listical Agents a ence with a New Tranquilizing Agent (Hydroxyphenamate). *Ibid*; *Davis, O.F.: On Use of Hydroxyphenamate in Anxiety Associated with Somatic Diseases. To be published; *Galexander, L.: Effect of Hydroxyphenamate on Conditional Psychogalvanic Reflex in Man, Supplement to Diseases of the Nervous System, Sept., 1961; *7Cahn, B.: Effect of Hydroxyphenamate in Treatment of Mild and Moderate Anxiety States. *Ibid*; *8Cahn, M. M., and Levy, E. J.: Use of Hydroxyphenamate (Listica) in Dermatological Therapy. *Ibid*; *9Eisenberg, B. C.: Amelioration of Allergic Symptoms with a New Tranquilizer Drug (Listica). *Ibid*; *19Friedman, A. P.: Pharmacological Approach to Treatment of Headache. *Ibid*; *11Greenspan, E. B.: Use of Hydroxyphenamate in Some Forms of Cardiovascular Disease. *Ibid*; *12Gouldman, C., Lunde, F., and Davis, J.: Clinical Trial of Hydroxyphenamate in Alcoholic Patients. *Ibid*; *13McLaughlin, B. E., Harris, J., and Ryan, E.: Double Blind Study Involving "Listica," Chlordiazepoxide, and "Placebo" as Adjunct to Supportive Psychotherapy in Psychiatric Clinic. *Ibid*; *14Bastian, J. W.: Pharmacology and Toxicology of Hydroxyphenamate. *Ibid*; *15Bossinger, C. D.: Chemistry of Hydroxyphenamate. *Ibid*.

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(without disturbing endocrine balance)



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both are free of pain-but only one is on

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swift, sure analgesia normally unmarred by nausea and vomiting

DILAUDID provides unexcelled analgesia in acute cardiovascular conditions. Onset of relief from pain is almost immediate. The high therapeutic ratio of DILAUDID is commonly reflected by lack of nausea and vomiting—and marked freedom from other side-effects such as dizziness and somnolence.

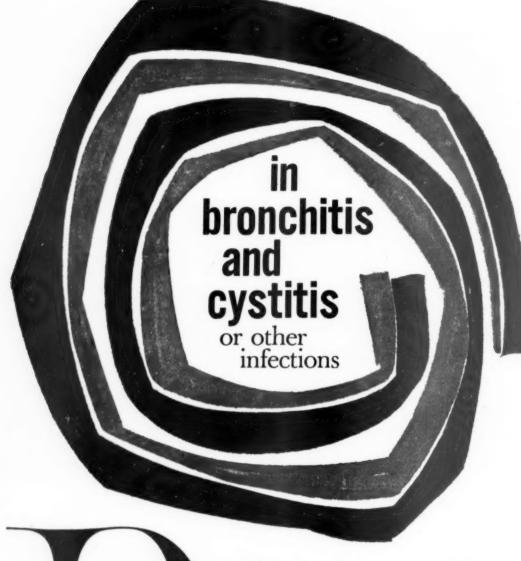
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CAPSULES, 150 mg., 75 mg. *Dosage*: Average infections—150 mg. four times daily. Severe infections—Initial dose of 300 mg., then 150 mg. every six hours.

PEDIATRIC DROPS, 60 mg./cc. in 10 cc. bottle with calibrated, plastic dropper. *Dosage:* 1 to 2 drops (3 to 6 mg.) per pound body weight per day—divided into four doses.

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PRECAUTIONS — As with other antibiotics, DECLO-MYCIN may occasionally give rise to glossitis, stomatitis, proctitis, nausea, diarrhea, vaginitis or dermatitis. A photodynamic reaction to sunlight has been observed in a few patients on DECLOMYCIN. Although reversible by discontinuing therapy, patients should avoid expo-sure to intense sunlight. If adverse reaction or idiosyn-crasy occurs, discontinue medication.

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Just as a medical instrument is engineered for maximum efficiency in performing its specific function, BENYLIN® EXPECTORANT is formulated to provide effective relief of cough associated with colds or allergy.

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BENYLIN EXPECTORANT is a pleasant-tasting, raspberry-flavored syrup...completely acceptable to patients of all ages.

supplied: BENYLIN EXPECTORANT is available in 16-ounce and 1-gallon bottles.

Each fluidounce contains: 80 mg. Benadryl Hydrochloride (diphenhydramine hydrochloride, Parke-Davis); 12 gr. ammonium chloride; 5 gr. sodium citrate; 2 gr. chloroform; 1/10 gr. menthol; and 5% alcohol. Indications: Relief of coughs due to colds, other symptoms associated with colds, and coughs of allergic origin. Dosage: Adults—1 to 2 teaspoonfuls every three to four hours. Children—½ to 1 teaspoonful every four hours. Precautions: Products containing Benadryl should be used cautiously with hypnotics or other sedatives; if atropine-like effects are undesirable; or if the patient engages in activities requiring alertness or rapid, accurate response (such as driving).

PARKE-DAVIS

PARKE, DAVIS & COMPANY, Detroit 32, Michigan

Unquestioned therapeutically ...long established clinically

A SEM

SUSPENSION

(chocolate-flavored)

For the many bacterial infections that respond promptly to triple sulfonamide therapy, Trisem presents a preferred formula.

Each 5 cc. contains, in a pleasant, chocolate-flavored vehicle:

Sulfamerazine (microcrystalline) 0.167 Gm. (2 3/5 gr.) Sulfadiazine (microcrystalline) 0.167 Gm. (2 3/5 gr.)

Sulfamethazine (microcrystalline) 0.167 Gm. (2 3/5 gr.)

Each 5 cc. (1 tsp.) provides 0.5 Gm. total sulfonamides.

Each 15 cc. (1 tbsp.) provides 1.5 Gm. total sulfonamides.

ADVANTAGES

- wide patient acceptability
- unquestioned therapeutic value
- high index of safety

- broad antibacterial spectrum
- provides high blood levels promptly
- economical for the patient

Many physicians prefer to use the sulfonamides to control bacterial infections because resistant organisms rarely develop. Nor, as with some broad spectrum therapy, is there the complication of such after-effects as moniliasis.

PACKAGING: In pint and gallon bottles.

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Can we measure the patient's comfort?

Not objectively, as activity of the heart can be measured electrocardiographically.

The higher level of relief reported with this new corticosteroid is a subjective thing that must be seen, by you, in your own patients.

Alphadrol*

Upjohn
75th year

See page 127 for description, indications, dosage, precautions, side effects, and how supplied.

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The editors of The American Journal of Surgery have prepared a special index covering the clinical reports on new operative technics and procedures as well as all of the other material published in the Journal during 1958, 1959 and 1960—a period that reflects dramatic advancements in many areas of surgery.

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Bottles of 30, 100 and 250.

- PAGE 821

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 A.M.A. Archives Int. Med. 100:750, 1957.

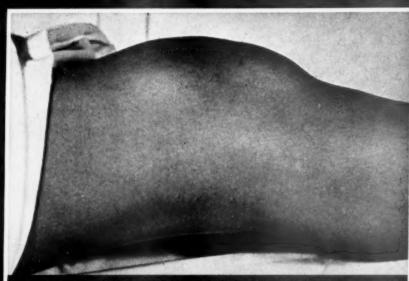
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PHARMACAL CORPORATION

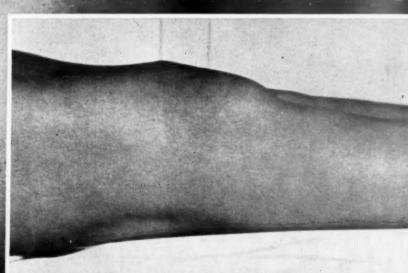
Lancaster Ave. at 51st Street, Philadelphia 31, Pa.

Also available: INJECTABLE QUINAGLUTE 10 cc. Vials, 0.08 Gm. Quinidine Gluconate per cc. *U.S. Patent 2895881



Female, Age 45. Diagnosis: Rheumatoid Arthritis, Class III, Stage III. Onset of disease was approximately 10 years ago. During this period, patient has never been asymptomatic. Various courses of cortisone therapy afforded partial relief. Immediately prior to institution of therapy with CELESTONE, there was swelling and or tenderness over both sternoclasticular joints, in shoulders, wrists, ankles, feet and the fingers which also has spindle-shaped deformities: limitation of motion in both knees. Considerable swelling with synovitis observed in right knee; patient unable to extend it fully when lying flat. Physical examination also revealed patient to be badly undernourished; there were no other significant findings. Rx. CELESTONE Tablets, 0.6 mg., q.i.d. Photo 1 shows patient prior to therapy with CELESTONE.

Arthritic inflammatory flare-up



Results: Within 48 hours, both subjective and objective improvement noted. Subsidence of pain began, and swelling substantially decreased. After 7 days, patient was completely asymptomatic and able to function normally in her environment. Dosage gradually reduced by weekly decrements of 0.3 mg, to a maintenance level of 0.3 mg, daily. Patient has remained asymptomatic, has gained 12 pounds and has returned to her normal weight. No side effects reported. Photo 2 shows patient after 7 days' therapy with CELESTONE Note 50 per cent decrease in knee size.

Photographs courtesy of Abraham Cohen, M.D., Philadelphia, Pa.



An important new agent for steroid therapy: Twenty months of pre-introductory clinical trials have demonstrated that Celestone provides unexcelled antiarthritic and anti-inflammatory effects with significantly lower milligram dosages than those required with most other steroids. These studies have also established its "low incidence of side effects...[and] absence of new toxic effects..."

Unsurpassed effectiveness in rheumatoid arthritis: In a series of 37 patients previously treated with other corticosteroids, Celestone was observed to produce an enhanced antiarthritic effect in over 50 per cent of the cases: "Better over-all improvement, as reflected in greater relief from pain, decreased inflammation, increased range of motion and constitutional benefits, was reported by the majority of patients in this series."²

In another group of patients studied, 88.8 per cent of whom were much improved or improved on Celestone, the authors noted that "results were not affected by either the class or the stage of rheumatoid arthritis; in fact, all but two of our Class III and Stage III patients obtained maximal improvement with betamethasone [Celestone]."

Rapid remission with Celestone

Gratifying results have been achieved with Celestone in a broad range of steroid-responsive disorders, from rheumatoid arthritis to bronchial asthma, allergic dermatoses, and inflammatory ocular diseases. Rapid subsidence of arthritic flare-up can usually be expected on average daily dosages of from 2 to 4 tablets. The single tablet strength (0.6 mg.) facilitates dosage schedules and proper adjustment when patients are switched from other corticosteroids.

CELESTONE "appears to satisfy the criteria for an improved corticosteroid in rheumatoid arthritis. It exerts

its antirheumatic and anti-inflammatory activity at lower dosages than other steroids available for the management of this disease...our data indicate that therapy with this steroid is attended by a substantially lower incidence of untoward effects...[and] has not been shown to cause any new side effects..."

For complete details, consult latest Schering literature available from your Schering Representative or the Medical Services Department, Schering Corporation, Bloomfield, New Jersey.

Cited References: 1. Frank, L.: The Place of Betamethasone in Dermatologic Practice, Paper presented at First Conference on the Clinical Application of Betamethasone—A New Corticosteroid, New York City, May 8, 1961. 2. Kammerer, W.H.: Observations on the Effects of Betamethasone in Rheumatoid Arthritis. Ibid. 3. Cohen, A., and Goldman, J.: Management of Rheumatoid Arthritis with a New Steroid. Ibid. Additional References: 4. Nierman, M. M.: The Use of Betamethasone in Dermatology. Ibid. 5. Gant, J. Q., Jr., and Gould, A. H.: Betamethasone: A Clinical Study. Ibid. 6. Dresner, E., and Catheart, E. S.: The Anti-Inflammatory Activity of Betamethasone, A New Glucocorticoid Epimer. Ibid. 7. Cecil, R. L.: Continued Progress in Corticosteroids. Ibid. 8. Bedell, H.: A New Systemic Steroid in the Treatment of Allergies in Office Practice. Ibid. 9. Goldman, L.: Investigation of a New Steroid in Dermatology. Ibid. 10. Hampton, S. F.: Betamethasone—A New Steroid in Allergy: A Preliminary Report. Ibid. 11. Bukantz, S. C.: Observations on the Use of Betamethasone in the Intractable Asthmatic Child. Ibid. 12. Schwartz, E.: Clinical Evaluation of Betamethasone in Chronic Intractable Bronchial Asthma. Ibid. 13. Gordon, D. M.: Betamethasone—A New Corticosteroid in Ophthalmology. Ibid. 14. Abrahamson, I. A., Jr.: A Clinical Evaluation of Betamethasone. Ibid. 18. 18.

(brand of betamethasone) Tablets, 0.6 mg.

GELESTONE a corticosteroid advance from Schering

not a generalpurpose antibiotic



Albamycin is not a broad-spectrum antibiotic, recommended for routine infections. It is specific for staphylococci (including resistant strains), and its use alone should (with the exceptions listed below) be limited to those cases in which staph is known or strongly suspected to be the causative organism.

Albamycin

- Albamycin is indicated in the treatment of staphy-

Indications — Albamycin is indicated in the treatment of staphylococcic infections, particularly in patients sensitive to other antibiotics or in the infections in which the organism is resistant to other antibiotics and sensitive to Albamycin, and in urinary tract infections due to microorganisms resistant to other commonly employed antibacterial agents but sensitive to Albamycin — notably certain strains of Proteus.

Administration and Dosage — Capsules and Syrup: The recommended dosage in adults is 500 mg, every twelve hours or 250 mg, every six hours, continued for at least forty-eight hours after the temperature has returned to normal and all evidence of infection has disappeared. In severe or unusually resistant infections, 0.5 Gm, every six hours or 1 Gm, every twelve hours may be employed. The dose for children is 15 mg, per kilogram of body weight per day for moderately acute infections; this may be increased to 30 to 45 mg, per kilogram of body weight per day for adults.

Parenteral: Intramuscularly—5 cc. of Albamycin solution may be used directly by slow injection deep into the gluteal muscle. Intravenously—it is recommended that 5 cc. of Albamycin solution solution of sodium chloride, Darrow's solution, or Ringer's solution and administered by intravenous infusion, or by diluting to a suitable quantity and administered by continuous drip infusion. Do not use with dextrese selution. When it is necessary to use a smaller volume intravenously, 5 cc. of Albamycin solution may be diluted to a minimum of 30 cc. with one of the above diluents and administered slowly over a period of five to ten minutes to avoid irritation of the vascular endothelium. The dosage for adults is 500 mg. Albamycin administered either intramuscularly

or intravenously every twelve hours. For children with moderately acute infections, the dosage is 15 mg. per kilogram of body weight per day. The daily dosage should be administered in two divided doses at intervals of twelve hours. As soon as the patient's condition permits, parenteral Albamycin should be replaced with oral Albamycin therapy.

Side Effects — Albamycin is a substance of low toxicity but is capable of inducing urticaria and maculopapular dermatitis. Leukopenia, which was rapidly reversible, has been reported in approximately 1% of cases. All of these side effects disappear rapidly upon discontinuance of the drug. In a certain few patients, a yellow pigment has been found in the plasma. This pigment is a metabolic by-product of the drug which, however, may interfere with determination of bilirubin and icteric index. Its presence is not associated with abnormal liver function tests or liver enlargement.

ence is not associated with abnormal liver function tests or liver enlargement.

Available — Albamycin, 500 mg., sterile, Mix-O-Vial.† Each Mix-O-Vial contains: 500 mg. Novobiocin (as novobiocin sodium), also 175 mg. Nicotinamide; 0.47 cc. N,N-Dimethylacetamide; 42.3 mg. Benzyl alcohol; 4.23 cc. water for injection. Albamycin Capsules. Each capsule contains: 250 mg. Novobiocin (as novobiocin sodium). Albamycin Syrup. 125 mg. per 5 cc. Each 5 cc. (one teapsonofful) contains: 125 mg. Novobiocin (as novobiocin calcium). Preserved with methylparaben, 0.075%, and propylparaben, 0.025%. "Trademark, Reg. U. S. Pat. Off. — The Upjohn brand of crystalline novobiocin sodium. †Trademark, Reg. U. S. Pat. Off.

The Upjohn Company Kalamazoo, Michigan

Upjohn



Kills pain....stops tension

For neuralgias, dysmenorrhea, upper respiratory distress, and postsurgical conditions—new compound of Soma, phenacetin and caffeine kills pain, stops tension, reduces fever—gives more complete relief than other analgesics...acts fast, relief lasts four to six hours

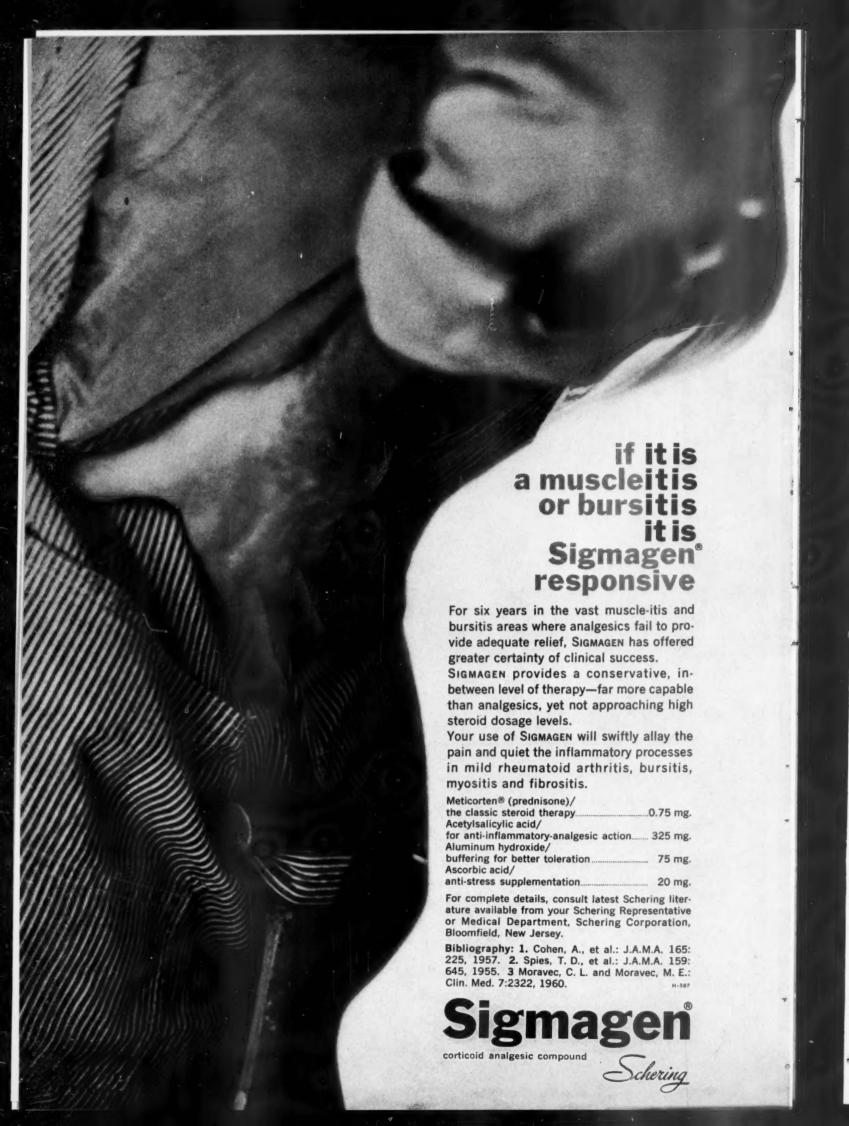
Composition: 200 mg. Soma (carisoprodol), 160 mg. phenacetin, 32 mg. caffeine. **Dosage:** 1 or 2 tablets q.i.d. **Supplied:** Bottles of 50 apricot-colored, scored tablets.

Also Available As SOMA COMPOUND + CODEINE

Soma Compound boosts the effectiveness of codeine. Soma Compound + Codeine

therefore contains only ¼ grain of codeine phosphate to relieve the more severe pain that usually requires ½ grain. Otherwise, its composition—and dosage—is the same as Soma Compound. Supplied in bottles of 50 white, lozenge-shaped tablets.

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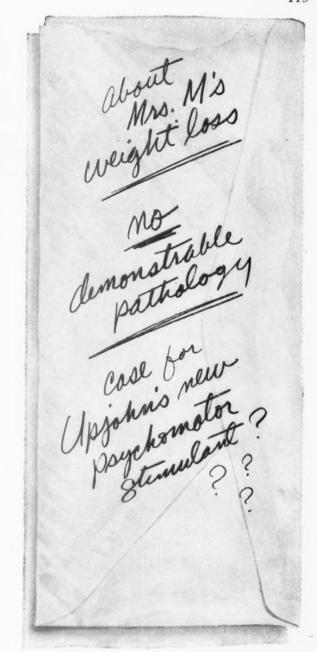
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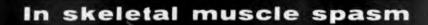
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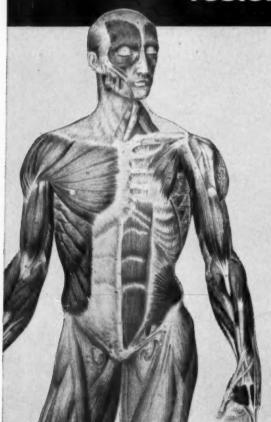


orphenadrine citrate 100 mg, tablets

quickly resolves the spasm...

relieves the pain...

restores normal function



Prolonged relief

may last up to 12 hours after administration . . . permits uninterrupted sleep at night . . . does not interfere with daytime alertness . . . only the muscles in spasm respond . . . no lessening of general muscle tonus.

Contraindications:

Routine precautions against use of anticholinergic drugs should be observed. Norflex should be used with caution in glaucoma, tachycardia, or urinary retention.

Simple dosage



for all adults regardless of age or sex: 2 tablets daily—one in the morning, one in the evening easily remembered . . . offers better patient cooperation.

NORFLEX is a product of



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(mebulamate, Wallace)

CENTRAL ACTING PRESSURE LOWERING AGENT

ANNOUNCING

CAPLA

A new drug that works in a new way
to control blood pressure
without serious side effects

Capla acts centrally at the brainstem vasomotor center

Reduces blood pressure by central action is not a ganglionic blocker

Capla is a new *kind* of drug to treat hypertension. Chemically, Capla is 2-methyl-2-sec-butyl-1, 3-propanediol dicarbamate. It is unrelated chemically to any other antihypertensive agent. Capla does not block ganglia, reduce blood volume or interfere with neurohormonal balance.

New therapy for hypertension

Because of its action at the brainstem vasomotor control center, Capla is a new therapy for hypertension. It is effective alone in the treatment of mild to moderate hypertension, and can be combined with diuretics or peripherally acting antihypertensives in more severe cases.

Exceptionally well tolerated

Capla acts rapidly, producing substantial blood pressure reduction within two hours, yet it does not produce postural hypotension. It has proved exceptionally well tolerated in clinical use and has no known contraindications. Capla has not produced changes in renal, hematological, hepatic or endocrine function. It is rapidly eliminated and has no cumulative effects.

Controls blood pressure without serious side effects

Capla does <u>not</u> produce depression, postural hypotension, nasal congestion or gastric hyperacidity Capla helps minimize one of the most difficult problems of hypertension therapy — unwanted and often serious side effects.

With Capla you have effective therapy without the unpleasant side effects which often cause patients to abandon treatment.

Side effects with Capla, when they do occur, are mild and usually transient. Transient drowsiness sometimes occurs, usually at higher dosage.

Mild calming effect

Patients on Capla often report a mild calming effect. This effect, together with the unusual freedom from serious side effects, makes therapy gratifying for both the patient and the physician.

Compatible with other drugs

Hypertensive patients with other disorders can receive Capla along with other medications.

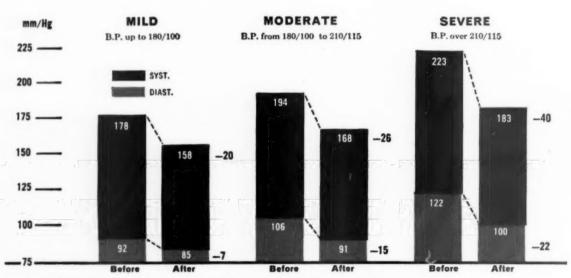
For example, patients with congestive heart failure, angina, and diabetes mellitus can receive Capla along with such medications as digitalis, nitrates, and insulin—without aggravating these other disorders.

Lowers blood pressure effectively in clinical use

CLINICAL & PHARMACOLOGICAL REPORTS

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Average Reductions In Systolic And Diastolic Blood Pressure Reported With Capla
(325 patients)



Usual dose, Capla 300 mg., q.i.d.—duration of therapy, 3 weeks to over 1 year.

These data show that Capla reduces both systolic and diastolic blood pressure, usually in proportion to initial pre-treatment elevations.

CAPLA

CENTRAL ACTING PRESSURE LOWERING AGENT



Wallace Laboratories Cranbury, New Jersey posage: the recommended dose of Capla is one 300 mg. tablet three or four times daily, before meals and at bedtime. The dosage should be adjusted to individual requirements; for example, older patients may require lower dosage.

COMPOSITION: each white, scored tablet contains 300 mg. of Capla (mebutamate, Wallace).

SUPPLIED: bottles of 100, scored tablets.

Literature and samples to physicians on request.

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Only 2 seconds are needed to write, "Thyroid Armour" on a prescription: a small investment in time, but one that offers big advantages to your patients. In Thyroid Armour you get maximum quality insured by consistently high standards of preparation. Over 75 years' experience is behind the Armour brand.

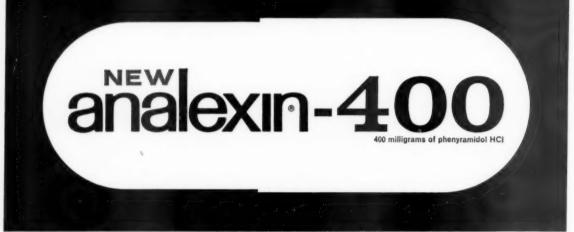
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EXCEEDINGLY EFFECTIVE "... The 85.1% incidence of effectiveness with the 400 mg. dose has exceeded the analgesic effectiveness of any other analgesic agent which we have studied to date, either alone or in combination....The utilization of higher doses for short periods of time indicates that the medication has a large therapeutic range, and this is reflected in the high incidence of effectiveness and low likelihood of untoward reactions.

"The practicing physician translating this into his own needs may be completely confident of using a medication with an excellent predictability and a safe analgesic response."1

EXTRAORDINARY MARGIN OF SAFETY. Analexin-400 is non-narcotic and not narcotic related; thus, it presents no danger of habituation or any other reaction associated with the frequent use of narcotics. Nor will Analexin-400 produce

sedation, mental confusion or depression occasionally observed with other analgesics or interneuronal blocking agents.1-23

INDICATIONS: Relief of pain in injury, low back pain, premenstrual cramping, dysmenorrhea, postoperative pain, and a wide variety of recurring and acute painful conditions.

DOSAGE: One capsule at onset of pain, followed by 1 capsule at intervals of 1 to 4 hours, as needed.

REFERENCES: From the Symposium, Recent Concepts of Pain and Analgesia, held in the Hall of States, American Hospital Association, Chicago, February 15, 1961: 1. Batterman, R. C.: Non-Narcotic Analgesia in Ambulatory Patients. 2. O'Dell, T. B.: Experimental Parameters in the Evaluation of Analgesics. 3. Miller, L. D.: Distribution, Excretion and Metabolic Fate of Phenyramidol. 4. Beisler, E.: Preliminary Report of Experience with Phenyramidol for Dental Analgesia. 5. Bader, G.: Preliminary Report on the Use of Analexin for Dysmenorrhea in Telephone Operators. 6. Taylor, S. L.: Phenyramidol in General Hospital Orthopedics. 7. Bodi, T.: Pain Management Among Clinic Outpatients. 8. Ramunis, J.: Experience of an Industrial Surgeon with Phenyramidol. 9. Kast, E. C.: Methodological Considerations in the Clinical Evaluation of an Analgesic. 10. Collopy, C. T.: Preliminary Comparisons of Two Non-Narcotic Analgesic Agents in Hospitalized Orthopedic Patients. 11. Cass, L. J.: Report on the Analgesic and Calmative Effectiveness of Two Preparations on Patients with Acute and Chronic Pain. 12. Lamphier, T. A.: Intravenous Phenyramidol in the Management of Low Back Pain and Allied Disorders. 13. O'Dell, T. B.: Chicago Med. 63:17, 1981. 15. Wainer, A. S.: J. Am. M. Women's A. 16:218, 1961. 16. Batterman, R. C.: Ann. New York Acad. Sc. 65:191, 1960. 18. O'Dell, T. B.: Ann. New York Acad. Sc. 65:191, 1960. 18. O'Dell, T. B.: Ann. Phenrascot. & Exper. Therap. 128:65, 1960. 19. O'Dell, T. B.; et al.: 4. Pharmacot. & Exper. Therap. 128:65, 1960. 19. O'Dell, T. B.; et al.: 9. Proc. 18:1694, 1959. 20. Gray, A. P., et al.: J. Am. Chem. Soc. 81:4347, 1959. 21. Wainer, A. S.: Clin. Med. 7:2331, 1960. 22. Clinical data in files of Medical Dept., Irwin, Neisler & Co., 1959. 23. Batterman, R. C., et al.: Am. J. Med. Sc. 238:315, 1959.

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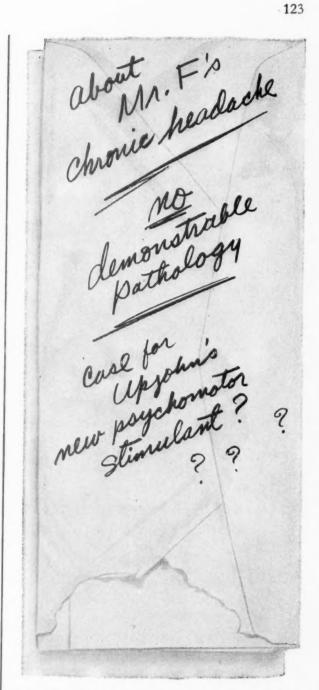
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EDWARD A. O'RORKE, Vice President

Sworn to and subscribed before me this 20th day of September, 1961. WALTER H. FREDRICKS [SEAL] Notary Public

(Commission expires March 30, 1962.)



FOR COMPLETE DETAILS ON



SEE PAGE 42-43



Excerpts from a 2-year study of 87 patients

USE OF DEPROL IN THE OFFICE TREATMENT OF DEPRESSION*

"Eighty-seven patients were studied during a period of over 2 years. All were psychoneurotic, and all were seen in private psychiatric practice. Although diagnoses differed, the most prominent symptom in each case was severe depression...Patients ranged in age from 16 to 70 years; the greater portion were 20 to 40 years old.

"The usual starting dosage of Deprol† was 1 tablet 4 times a day... If necessary, this dosage was increased to 6 tablets per day, and then to 8."

Results

"All except 2 of the 87 patients treated with Deprol were definitely helped by this medication.

"Deprol was found most useful in patients with pronounced depressions characterized by apathy, withdrawal, and inability to perform. Such patients were relieved of their oppressive despondency and crying spells and became accessible to psychotherapy. They became more hopeful and more willing and able to expend effort to help themselves. They were able to sleep well, to enjoy their food again, to concentrate better, to make decisions and to return to normal activity...

"Unlike most other drugs used for depression, [Deprol] is also effective in controlling a wide spectrum of associated symptoms, particularly anxiety, tension, sleep disturbances, and psychosomatic complaints. Deprol does not depress appetite but permits its normal return as the patient improves. It is not a euphoriant; rather, patients taking the drug experience a return to a stable and normal mood."

Side Effects and Toxicity

During the two years of this study "... no side-effects were observed. Two patients who attempted suicide by ingesting, respectively, 40 and 30 tablets of Deprol experienced prolonged sleep with slight, transient fall in blood pressure, but they recovered without treatment and without sequelae."

Conclusion

"Deprol marks a definite step forward in the safe and effective treatment of depression."

*Ruchwarger, A.: M. Ann. District of Columbia 28:438, Aug. 1959. †Supplied by WALLACE LABORATORIES, Cranbury, N. J.

'Deprol'®

Dosage: Usual starting dose is 1 tablet q.i.d. When necessary, this may be increased gradually up to 3 tablets q.i.d. With establishment of relief, the dose may be reduced gradually to maintenance levels.

Composition: 1 mg. 2-diethylaminoethyl benzilate hydrochloride (benactyzine HCl) and 400 mg. meprobamate.

Supplied: Bottles of 50 light-pink, scored tablets.

"wearability"





MAALOX

(MARNESIUM-ALUMINUM NYDROXIDE GEL)

ANTACID - DEMULCENT NON-CONSTIPATING

A colloidal suspension of Magnesium and Aluminum Hydroxides useful for the relief of gastric hyperacidity.

Shake Well Before Using

Section. Two to four teaspoonfuls may be given in water or milk twenty minutes after meals and at bediene. Use an directed by your physician. Maioli not be used in patients who are severely debilitated or suffering from Ridney failure.

KEEP FROM FREEZING 34772

WILLIAM H. RORER, Inc.

NO TASTE FATIGUE EXCELLENT RESULTS NO CONSTIPATION

the most widely prescribed and most wearable of all antacids suspension tablets

Tablet Maalox No. 1 equivalent to 1 teaspoon Suspension Tablet Maalox No. 2 equivalent to 2 teaspoons Suspension



Can we measure the patient's comfort?

The physician can measure activity of the heart by means of electrocardiography. But he has no instrument—no objective test—for measuring comfort.

For this, he must depend upon his own powers of observation and the patient's own description of how he feels.

Because these are, admittedly, subjective criteria, the validity of results hinges entirely on the experience and objectivity of the investigators involved.

Such well-qualified clinicians have reported that a new corticosteroid developed in research laboratories of Upjohn actually raises the level of relief obtainable with this type of therapy.

This difference cannot be "proved." It must be seen. And the only practical way for you to do this is to evaluate this new drug critically in your own practice. Please do, at your first opportunity. We are confident that you will be glad you did.

The new corticosteroid from Upjohn research

Each tablet contains Alphadrol (fluprednisolone) 0.75 mg. or 1.5 mg. Supplied in bottles of 25 and 100.

The anti-inflammatory activity of Alphadrol is comparable to the best effects obtained in current practice. Results obtained with Alphadrol have been such as to warrant classifying it among the most efficient steroids now available.

More than twice as potent as prednisolone, Alphadrol exhibits no new or bizarre side effects. Salt retention, edema or hypertension, potassium loss, anorexia, muscle weakness or muscle wasting, excessive appetite, abdominal cramping, or increased abdominal girth have not been a problem.

Indications and effects

The benefits of Alphadrol (anti-inflammatory, antiallergic, antirheumatic, antileukemic, antihemolytic) are indicated in acute rheumatic carditis, rheumatoid arthritis, asthma, hay fever and allergic disorders, dermatoses, blood dyscrasias, and ocular inflammatory disease involving the posterior segment.

Precautions and contraindications

Patients on Alphadrol will usually experience dramatic relief without developing such possible steroid side effects

as gastrointestinal intolerance, weight gain or weight loss, edema, hypertension, acne or emotional imbalance.

As in all corticotherapy, however, there are certain pre-cautions to be observed. The presence of diabetes, osteo-porosis, chronic psychotic reactions, predisposition to thrombophlebitis, hypertension, congestive heart failure, renal insufficiency, or active tuberculosis necessitates care-ful control in the use of steroids. Like all corticosteroids, Alphadrol is contraindicated in patients with arrested tuberculosis, peptic ulcer, acute psychoses, Cushing's syndrome, herpes simplex keratitis, vaccinia, or varicella.

because DIABETES IS FOR LIFE start with Diabinese*

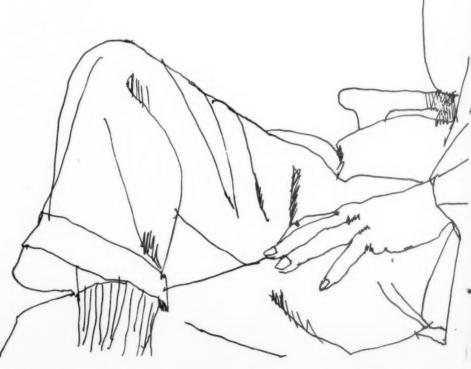
for maximum assurance of continuing success with oral therapy

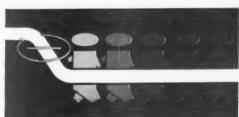
long-term use continues to demonstrate that DIABINESE

has a comparatively low incidence of secondary failures.

provides maximum convenience and economy because of once-a-day oral administration.

at presently recommended dosage has a low incidence of adverse effects which require discontinuance of therapy. See "In Brief."





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abinese® BRAND OF CHLORPROPAMIDE

the oral antidiabetic most likely to succeed

economical once-a-day dosage



IN BRIEF

DIABINESE, a potent sulfonylurea, provides smooth, long-lasting control of blood sugar permitting economy and simplicity of low, once-a-day dosage. Moreover, DIABINESE often works where other agents have failed to give satisfactory control.

INDICATIONS: Uncomplicated diabetes mellitus of stable, mild or moderately severe nonketotic, maturity-onset type. Certain "brittle" patients may be helped to smoother control with reduced insulin requirements.

ADMINISTRATION AND DOSAGE: Familiarity with criteria for patient selection, continued close medical supervision, and observance by the patient of good dietary and hygienic habits

As with insulin, DIABINESE dosage must be regulated to individual patient requirements. Average maintenance dosage is 100-500 mg. daily. For most patients the recommended starting dose is 250 mg. given once daily. Geriatric patients should be started on 100-125 mg. daily. A priming dose is not necessary and should not be used; most patients should be maintained on 500 mg. or less daily. Maintenance dosage above 750 mg. should be avoided. Before initiating therapy, consult complete dosage

SIDE EFFECTS: In the main, side effects, e.g., hypoglycemia, gastrointestinal intolerance, and neurologic reactions, are related to dosage. They are not encountered frequently on presently recommended low dosage. There have been, however, occasional cases of jaundice and skin eruptions primarily due to drug sensitivity; other side effects which may be idiosyncratic are occasional diarrhea (sometimes sanguineous) and hematologic reactions. Since sensitivity reactions usually occur within the first six weeks of therapy, a time when the patient is under very close supervision, they may be readily detected. Should sensitivity reactions be detected, DIABINESE should be discontinued.

PRECAUTIONS AND CONTRAINDICATIONS: If hypoglycemia is encountered, the patient must be observed and treated continuously as necessary, usually 3-5 days, since DIABINESE is not significantly metabolized and is excreted slowly. DIABINESE as the sole agent is not indicated in juvenile diabetes mellitus and unstable or severely "brittle" diabetes mellitus of the adult type. Contraindicated in patients with hepatic dysfunction and in diabetes complicated by ketosis, acidosis, diabetic coma, fever, severe trauma, gangrene, Raynaud's disease, or severe impairment of renal or thyroid function.

DIABINESE may prolong the activity of barbiturates. An effect like that of disulfiram has been noted when patients on DIABINESE drink alcoholic beverages.

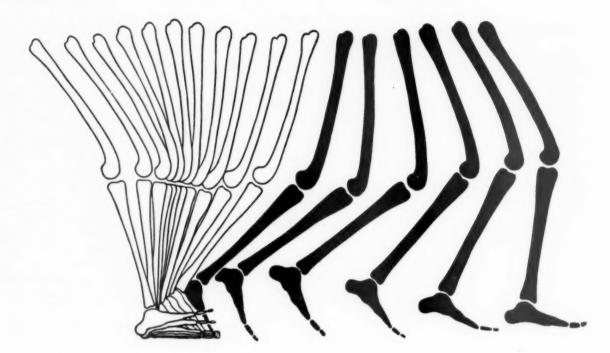
SUPPLIED: As 100 mg. and 250 mg. scored chlorpropamide

More detailed professional information available on request.

Science for the world's well-being®



PFIZER LABORATORIES (12er) Division, Chas. Pfizer & Co., Inc. New York 17, New York



Depo-Medrol was administered intra-articularly to 118 patients (250 injections) for disorders including rheumatoid arthritis, osteoarthritis, epicondylitis, and tendinitis.

Relief of pain and swelling was marked or complete in 104 of the 118 (88.1%); duration of response to a single injection was more than three weeks in 89 patients (75.4%) and more than six weeks in 39 of these. "Post-injection flare-up was practically non-existent."

Indications and dosages

Intra-articular, intrabursal and intratendinous injections of Depo-Medrol are useful for sustained anti-inflammatory effect and symptomatic relief in rheumatoid arthritis, osteoarthritis, bursitis, tendinitis, epicondylitis and other rheumatic disorders.

rheumatoid arthritis, osteoarthritis, bursitis, tendinitis, epicondylitis and other rheumatic disorders.

Intra-articular dosage depends on the size of the joint and the severity of the condition. Injections may be repeated, if necessary, at intervals of one to five weeks. A suggested dosage guide: Large joint, 20 to 80 mg.; medium joint, 10 to 40 mg.; small joint, 4 to 10 mg.

4 to 10 mg.

For administration directly into bursae, dosage may be 4 to 30 mg. (repeat injections are usually not needed).

For injection into the tendon sheath,

For injection into the tendon sheath, 4 to 30 mg. is a usual range (in recurrent or chronic conditions, repeat injections may be needed).

Precautions

Depo-Medrol for local effect is contraindicated in the presence of acute infectious conditions. Infrequently, atrophic changes in the dermis may form shallow depressions in the skin at the injection site, but these usually disappear in a few months.

 Norcross, B. M., and Winter, J. A.: Methylprednisolone acetate: a single preparation suitable for both intraarticular and systemic use, New York J. Med. 61:552 (Feb. 15) 1961.

*Trademark, Reg. U. S. Pat. Off. methylprednisolone acetate, Upjohn

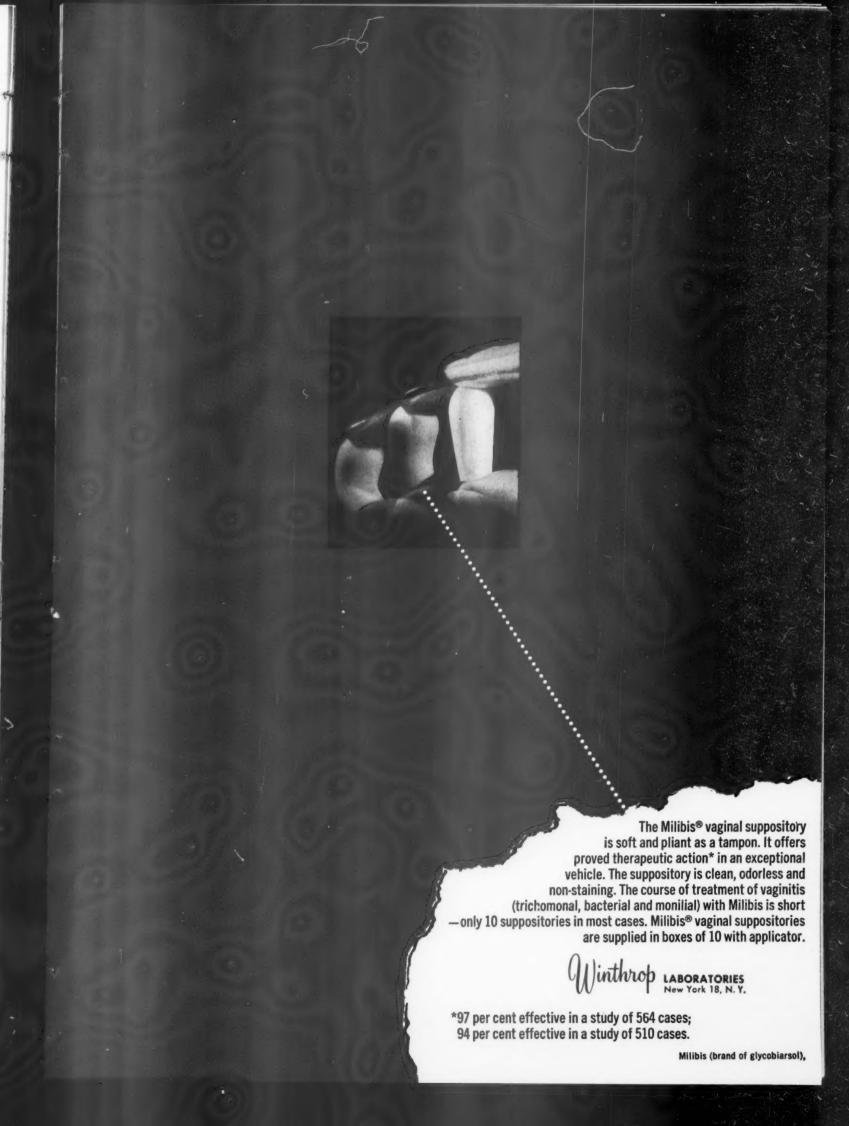
The Upjohn Company, Kalamazoo, Michigan

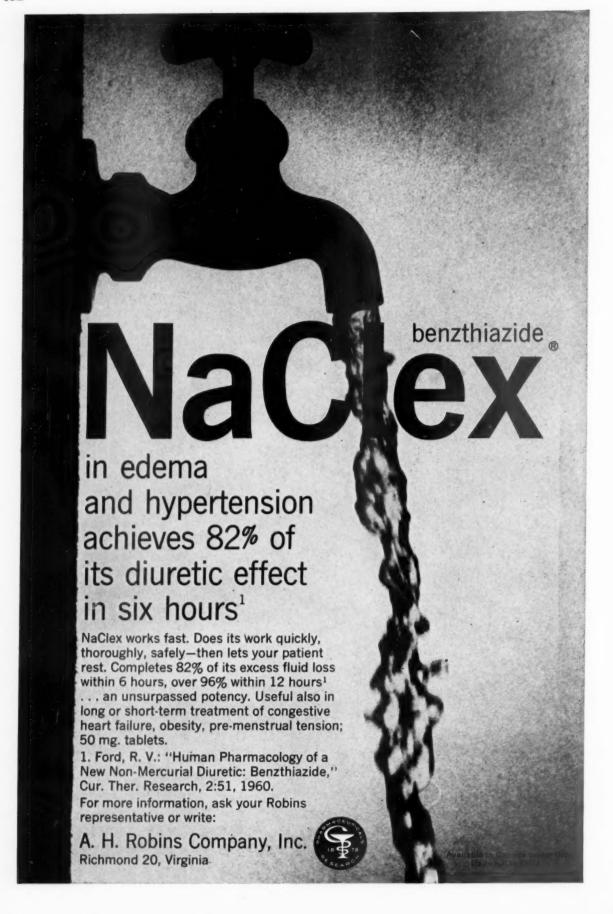
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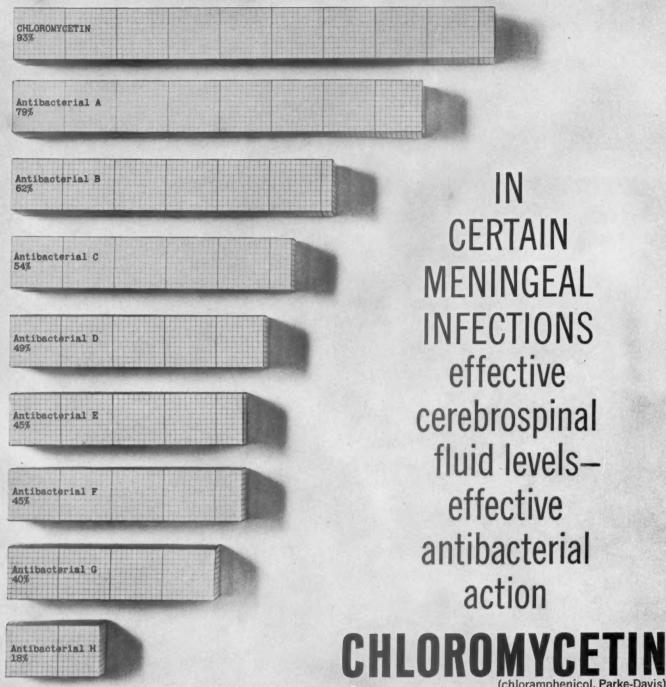
relief within hours... lasting for weeks

Depo-Medrol^{*} intraarticularly

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in vitro sensitivity of Hemophilus influenzae to CHLOROMYCETIN and to eight other antibacterials*

Sensitivity tests were done by the disc method on a total of 100 strains of *H. influenzae* obtained on clinical isolates from 1955 through 1958.

*Adapted from Jolliff, C. R.; Engelhard, W. E.; Ohlsen, J. R.; Heidrick, P. J., & Cain, J. A.: Antibiotics & Chemother. 10:694, 1960, with permission of the authors.

CHLOROMYCETIN (chloramphenicol, Parke-Davis) is available in various forms, including Kapseals® of 250 mg., in bottles of 16 and 100.

See package insert for details of administration and dosage.

Warning: Serious and even fatal blood dyscrasias (aplastic anemia, hypoplastic anemia, thrombocytopenia, granulocytopenia) are known to occur after the administration of chloramphenicol. Blood dyscrasias have occurred after both short-term and prolonged therapy with this drug. Bearing

in mind the possibility that such reactions may occur, chloramphenical should be used only for serious infections caused by organisms which are susceptible to its antibacterial effects. Chloramphenical should not be used when other less potentially dangerous agents will be effective, or in the treatment of trivial infections such as colds, influenza, or viral infections of the throat, or as a prophylactic agent.

Precautions: It is essential that adequate blood studies be made during treatment with the drug. While blood studies may detect early peripheral blood changes such as leukopenia or granulocytopenia, before they become irreversible,

such studies cannot be relied upon to detect bone marrow depression prior to development of aplastic anemia.

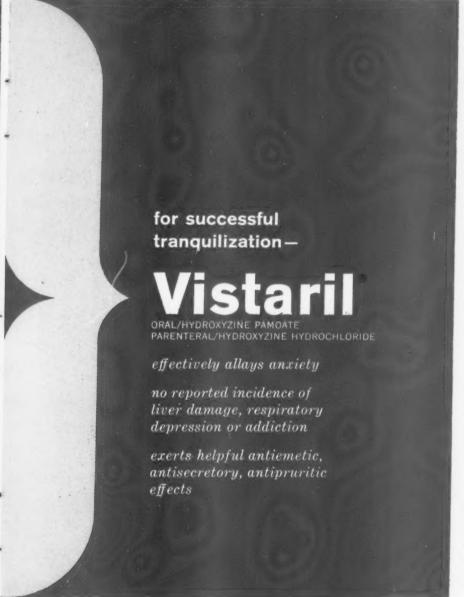
PARKE-DAVIS

PARKE, DAVIS & COMPANY, Detroit 32, Michigen

Notable Success with VISTARIL...

reduces narcotic reallays anxiety without in quirements and inciimpairing ability to prepartum dence of narcoticcooperate during tension induced respiratory labor and delivery1 depression, helps and control emesis1,4 anxiety helps correct certain in the allays anxiety without functional arrhythadverse influence on cardiac blood pressure² mias, does not inor the crease gastric secretion² hypertensive patient produces no signifiallays anxietymakes patient more cant depression of blood pressure, pulse manageable3 problem rate, or respiration. No liver involvement drinkers reported allays anxiety without reduces incidence of depression of vital narcotic-induced repreoperative functions4 spiratory depression tension and hypotension, relaxes skeletal muscle. and smooths recovery and anxiety helps control emesis4 allays tension in agiavoids danger of liver tated, hyperkinetic damage or other untoward reactions patients pediatrics

References: 1. Benson, C., and Benson, R. C.: Scientific Exhibit, Illinois Acad. Gen Practice, Sept., 1960. 2. Salmons, J. A.: Dis. Chest 38:105, 1960. 3. Major, R. A.: GP 21:104, 1960. 4. Grady, R. W., and Rich, A. L.: Scientific Exhibit, Am Soc. Anesth, New York, Oct. 4-7, 1960.



Science for the world's well-being®



PFIZER LABORATORIES Division, Chas. Pfizer & Co., Inc. Brooklyn 6, New York

IN BRIEF

Vistaril is hydroxyzine pamoate. The hydrochloride salt of hydroxyzine is used in the parenteral solution.

Vistaril acts rapidly in the symptomatic treatment of a variety of neuroses and other emotional disturbances manifested by anxiety, apprehension or fear-whether occurring alone or complicating a physical illness. Used preoperatively and prepartum, Vistaril controls anxiety and fear, permits a substantial reduction in the amount of meperidine or other narcotic required for satisfactory analgesia, and helps prevent emesis. Vistaril's calming effect usually does not impair discrimination, and is accompanied by direct and secondary muscle relaxation. No toxicity has been reported with Vistaril, and it has a remarkable record of freedom from reactions. INDICATIONS: Vistaril is clinically effective

in anxiety and tension states, senility, anxiety associated with various disease states, alcoholism, pre- and postpartum and pre- and postoperative tension and emesis, certain functional arrhythmias, and pediatric behavior problems.

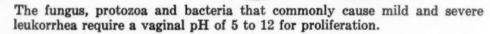
ADMINISTRATION AND DOSAGE: Dosage varies with the state and response of each patient, rather than with weight and should be individualized by the physician for optimum results. Recommended oral dosage: In anxiety and tension states, senility, alcoholism, pre- and postoperative and pre- and postpartum tension and emesis: up to 400 mg. daily in divided doses. In anxiety associated with asthma, neurodermatoses, menopausal syndrome, digestive disorders, functional or essential hypertension, tension headaches: 50 mg. q.i.d. initially - adjust according to response. In cardiac arrhythmias: initial - 25 mg. q. 6 h. until arrhythmia disappears; maintenance or prophylactic-50-75 mg. daily in divided doses. In pediatric behavior problems under 6 years: 50 mg. daily in divided doses. Six and over: 50-100 mg. daily in divided doses. Recommended parenteral dosage: In preoperative, obstetrical, and more emergent situations in other indications: 25-100 mg. I.M. or I.V. q. 4 h., p.r.n. In cardiac arrhythmias: 50-100 mg. I.M. stat, and q. 4-6 h., p.r.n.; maintain with 25 mg. b.i.d. or t.i.d. SIDE EFFECTS: Drowsiness may occur in some patients; if so, it is usually transitory, disappearing within a few days of continued therapy or upon reduction of dosage. Dryness of mouth may be encountered at higher doses.

PRECAUTIONS: The potentiating action of hydroxyzine should be taken into account when the drug is used in conjunction with central nervous system depressants. Do not exceed 1 cc. per minute I.V. Do not give over 100 mg. per dose I.V. Parenteral therapy is usually for 24-48 hours, except when, in the judgement of the physician, longer-term therapy by this route is desirable.

SUPPLIED: VISTARIL Capsules (hydroxyzine pamoate) -25, 50, and 100 mg. VISTARIL Oral Suspension (hydroxyzine pamoate) - 25 mg. per 5 cc. teaspoonful. VISTARIL Parenteral Solution (hydroxyzine hydrochloride) -10 cc. vials, 25 mg. per cc.; 2 cc. ampules, 50 mg. per cc.

More detailed professional information available on request.

Hostile Environment...



In Vialland

Trimagill creates a hostile environment! It produces a pH of 2.0 to 2.5—the three principal infecting organisms cannot live in this acid range.

Trimagill is well tolerated and has been proved effective in thousands of cases of leukorrhea, vaginitis, cervicitis, moniliasis and mixed infections. No untoward reactions that would require discontinuation of treatment were reported. At times denuded mucous membranes are so irritated that Trimagill may give a temporary burning sensation. This is usually short lived.

Trimagill does not foster resistant mutants or result in monilia overgrowth. Trimagill may be used during menstruation.

CONTENTS: Tartaric Acid, Citric Acid, Boric Acid, Dextrose, Potassium Alum, Potassium Bitartrate and Adhesives.

SUPPLIED: <u>Powder:</u> 5-oz. Plastic Insufflator Bottles; <u>Vaginal Inserts:</u> Boxes of 24. NOTE: Consult package circular for information on dosage and instructions for use.

Write for descriptive literature.



TRIMAGILL

POWDER . VAGINAL INSERTS

THE S. E. MASSENGILL COMPANY

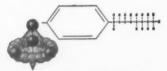
Bristol, Tennessee • New York • Kansas City • San Francisco

Why is the methyl "governor" in Orinase important?

One of the most significant advantages of Orinase therapy is the rarity of associated hypoglycemic reactions.

This widely-reported clinical benefit is a function of the exclusive Orinase methyl "governor." Lending itself to ready oxidation (principally, it is thought, a hepatic process), the methyl group ensures prompt metabolic inactivation of the Orinase molecule. What actually happens is that a rapidlyand continuously-excreted carboxy-metabolite is produced that has no hypoglycemic activity at the existing levels.

As a result of the oxidation of its methyl group, Orinase shows a decline in activity soon after it reaches its effective peak in the plasma. Maintenance dosage serves to reduce blood sugar levels to normal, but rarely below that point, and there is no reported problem of accumulation.



An exclusive methyl "governor" minimizes hypoglycemia

Indications and effects: The clinical indication for Orimase is stable diabetes mellitus. Its use brings and effects of blood sugar; glycosuria diminishes, and such symptoms as pruritus, polyuria, and polyphagia disappear.

Dosage: There is no fixed regimen for initiating Orimase therapy. A simple and effective method is as follows: First day—6 tablets; second day—4 tablets; third day—2 tablets. The daily dose is then adjusted—raised, lowered or maintained at the two-tablet level, whichever is necessary to maintain optimum control.

Patients receiving insulin fless than 20 units)—discontinue insulin and institute Orimase; (20 to 10 to 50% reduction in insulin dose with a further careful reduction as response to Orimase is observed; (more than 40 units)—reduce insulin by 20% and initiate Orimase are promoted from the control of the careful reduction in insulin dosage as response to Orimase is observed. In candidates for combined Orimase-like observed.

more weeks.

Contraindications and side effects: Orinase is contraindicated in patients having juvenile or growth-onset, unstable or brittle types of diabetes trauma or gangrene.

Gide effects are mild, transient and limited to approximately 3% of patients. Hypoglycemia and toxic reactions are extremely rare. Hypoglycemia is most likely to occur during the period of transition from insulin to Orinase. Other untoward Copyright 1961, The Upjohn Company

reactions to Orinase are usually not of a serious nature and consist principally of gastrointestinal disturbances, headache, and variable allergic skin manifestations. The gastrointestinal disturbances (nausea, epigastric fullness, heartburn) and headache appear to be related to the size of the dose, and they frequently disappear when dosage is reduced to maintenance levels or the total daily dose is administered in divided portions after meals. The allergic skin manifestations (pruritus, erythems, and urticarial, morbilitorm, or maculopapitems, and urticarial and urticari

Orinase should be discontinued.

Clinical toxicity: Orinase appears to be remarkably free from gross clinical toxicity on the basis of experience accumulated during more than four years of clinical use. Crystalluria or other untoward effects on renal function have not been observed. Long-term studies of hepatic function in humans and experience in over 650,000 dias betics have shown Orinase to be remarkably free of hepatic toxicity. There has been reported only odministration estatic fauncies related to Orinase pre-existing liver disease and which rapidly reversed upon discontinuance of the drug.

Each tablet contains:

Tolbutamide

O.5 Gm.

Supplied: In bottles of 50.

*Trademark, Reg. U.S. Pat. Off.--tolbutamide, Upjohn June. 1961

Upjohn



With proper medical management and adequate control of seizures, epileptic persons may lead productive, functioning lives. 1.2 To implement this goal, many clinicians have come to rely on DILANTIN for outstanding control of grand mal and psychomotor attacks. Such efficacy was demonstrated in a state hospital where "... incidence of grand mal seizures was fairly constant at 7000 to 8000 seizures per year. Within a few months after the introduction of DILANTIN Sodium, the seizure rate fell to around 250 per year, without any other significant change in the

program." DILANTIN Sodium (diphenylhydantoin sodium, Parke-Davis) is available in several forms, including Kapseals, 0.03 Gm. and 0.1 Gm., bottles of 100 & 1,000.

DILANTIN HELPS HER SHARE IN THE GOOD THINGS OF LIFE

other members of the PARKE-DAVIS FAMILY OF ANTICONVULSANTS for grand mal and psychomotor seizures: Phelantin® Kapseals (Dilantin 100 mg., phenobarbital 30 mg., desoxyephedrine hydrochloride 2.5 mg.), bottles of 100; for the petit mal triad: Milontin® Kapseals (phensuximide, Parke-Davis), 0.5 Gm., bottles of 100 and 1,000 and Suspension, 250 mg. per 4 cc., 16-ounce bottles · Celontin® Kapseals (methsuximide, Parke-Davis), 0.3 Gm., bottles of 100 · Zarontin® Capsules (ethosuximide, Parke-Davis), 0.25 Gm., bottles of 100. See medical brochure for details of administration, precautions, and dosage.

(1) Carter, S.: M. Clin. North America 37:315, 1953. (2) Maltby, G. L.: J. Maine M. A. 48:257, 1957. (3) Thomas, M. H., in Green, J. R., & Steelman, H. F.:
Epileptic Seizures, Baltimore, The Williams & Wilkins
Company, 1956, p. 43.

THIS ART STUDENT HAS EPILEPSY...



clinical experience continues to corroborate the range and efficacy of



CYTOTOXIC AGENT for palliative chemotherapy of certain types of malignant neoplasms

Cytoxan demonstrated therapeutic advantage over other agents in a recent 12-month study* of 130 patients, most of whom were refractory to previous treatment:

DISEASE	NUMBER OF	RESULTS				INADEQUATE
	PATIENTS	GOOD FAIR		TRANSIENT	FAILURE	TRIAL
Lymphoma	74	34 3 10 3 15 0	3	5	23 9 3	9 3 3
Hodgkin's Disease	29		3	4 0		
Lymphosarcoma	21		0			
Multiple Myeloma	16	9	0	0	4	3
Reticulum Cell Disease	8 0	0	0 0	1	7 8 3	0 5 1 3
Leukemia	23	10 0 4 0 5 0	0	0		
Chronic Lymphatic Leukemia	8		0	0		
Acute Monoblastic Leukemia	11		0			
Acute Myeloblastic Leukemia	te Myeloblastic Leukemia 4 1 0	0	0	2	1	
Carcinoma (Breast, Lung, and Solid Tumors)	29	2	1	1	23	2
Miscellaneous (Mycosis, Fungoides, Psoriasis)	4	0	0	1	3	0
Total	130	46	4	7	57	16

^{*}Adapted from Wall, R. L., and Conrad, F. G.*

Note that the neoplastic disorders most responsive to Cytoxan were lymphosarcoma, multiple myeloma, Hodgkin's disease, and chronic lymphatic leukemia. Occasionally, good results were observed in acute monocytic leukemia and carcinoma of the breast.

Other advantages noted in this study*

- multiple routes of administration, permitting prolonged maintenance therapy lack of latency period for bone marrow depression failure to produce significant thrombocytopenia potential therapeutic effect in diseases usually unresponsive to other mustard compounds (e.g., myeloma).
- *Wall, R. L., and Conrad, F. G.: Arch. Int. Med. 108:456-482, 1961.

INDICATIONS: Cytoxan is valuable for palliative therapy of certain malignant neoplasms, particularly some of those arising in the reticuloendothelial and hematopoietic systems and certain solid tumors.

Types of cancer which have proved relatively more susceptible or more resistant to Cytoxan therapy may be

grouped as follows: Group I: Neoplasms relatively susceptible to Cytoxan

Hodgkin's disease Lymphomas: lymphosarcoma; giant follicular lymphoma; reticulum cell sarcoma

Leukemia: acute; chronic

Mycosis fungoides

Group II: Neoplasms relatively resistant to Cytoxan Malignant neoplasms of the breast and the ovary*

Malignant neoplasms of the lung, the gastrointestinal tract and the genitourinary system, including the cervix and the uterus

Malignant neoplasms of miscellaneous origin

Malignant melanomas

*Malignant tumors of these organs are somewhat more susceptible to Cytoxan therapy than are the others included

in this group. DOSAGE: For neoplasms relatively susceptible to Cytoxan - Patients with lymphomas and other neoplasms believed to be relatively susceptible to Cytoxan therapy are given an initial dose of 2 to 3 mg./Kg./day intravenously. White blood counts and platelet determinations should be made daily or twice weekly and the dosage adjusted accordingly. Intravenous infusions should be continued for at least 6 days unless otherwise indicated. A leukopenia of between 1500 and 5000 cells per cu. mm. (or lower) may be expected between the tenth and fourteenth day. In the presence of a leukopenia of less than 2000/cu. mm. Cytoxan should be discontinued until the white cell count returns to 2000 to 5000 (usually within a week). Dosage is subsequently adjusted as indicated by the patient's objective response and the leukocyte count. If the patient is subjectively improved, if the size of the tumor has decreased, or if the white cells are satisfactorily maintained between 2000 and 5000/cu. mm. oral dosage may be instituted equivalent to intra-

venous dosage. Thrombocytopenia is rarely observed on this regimen. If platelet counts of less than 100,000/cu. mm. are observed, the patient should be watched carefully. If platelets continue to decrease, Cytoxan should be discontinued.

The patient who has had previous treatment with alkylating agents, or x-ray, or is debilitated may be more susceptible to bone marrow depression, and initial Cytoxan doses should be more conservative than the above. Such patients should have more frequent hematologic evaluation. Good medical practice demands access to a reliable hematologic laboratory when using Cytoxan.

For neoplasms relatively resistant to Cytoxan-Patients with carcinomas and other malignant neoplasms believed to be less susceptible to Cytoxan therapy are given a dose of 4 to 8 mg./Kg./day intravenously. Unless there are indications to the contrary, this dose is continued for 6 days, then stopped. Leukopenia usually ensues on the tenth to fourreduction is not common, and platelets may actually increase. The leukocyte count promptly returns toward normal levels in most cases, and as it begins to increase, sufficient Cytoxan is administered to maintain it near 2000 to 5000/cu, mm. This may be accomplished by two intravenous injections weekly, or by oral administration, or by a combination of both routes. An oral dosage of 50 to 200 mg. daily or an intravenous injection of 5 mg./Kg. twice weekly will usually suffice.

The platelet and leukocyte counts should be followed carefully, and the prior treatment history of patients carefully evaluated as delineated above.

Leukopenia as a guide to adequacy of dosage—The best objective measure for dosage seems to be the number of circulating white blood cells. This is used as an index of the activity of the hematopoietic system, especially the bone marrow. The mechanism by which Cytoxan causes a reduction in the level of white blood cells is not known, but cessation of dosage results in an increase in the level, indicating that the hematopoietic system had not been permanently affected. When large doses (8 mg./Kg./day for 6 days) are given initially, the white cell count falls rapidly. Following the cessation of the 6-day course, the white cells may continue to decline for as long as 8 days and then increase. The reduction of the white cell count during Cytoxan therapy and its subsequent increase when therapy is discontinued can be repeated in the same patient.

Maximal reduction in leukocyte count indicates the maximal permissible Cytoxan level for therapeutic effect. Leuko penic patients must be watched carefully for evidence of

Total white blood cell and thrombocyte counts should be obtained 2 or more times weekly in order to evaluate

therapy and to adjust dosage.

SIDE EFFECTS: Although Cytoxan is related to nitrogen mustard, it has no vesicant effect on tissue. It does not traumatize the vein when injected intravenously, nor does it cause any localized tissue reaction following extravasation. It may be administered intravenously, intramuscularly, intraperitoneally, intrapleurally or directly into the tumor, when indicated. It is apparently active by each of these

Nausea and vomiting are common and depend on dose and on individual susceptibility. However, many investigators accept the nausea and vomiting in favor of maintaining maximal therapy. The vomiting can be controlled

with antiemetic agents.

Alopecia is a frequent side reaction to Cytoxan therapy. It has been observed in 28% of the patients studied in this country. The incidence is greater with larger doses. The loss of hair may first be noted about the 21st day of therapy and may proceed to alopecia totalis. This-effect is reversed following discontinuance of Cytoxan; during reduced maintenance therapy, hair may reappear. It is essential to advise the patient in advance concerning this effect of the drug.

Dizziness of short duration and of minor degree has

occasionally been reported.

Leukopenia is an expected effect and can be used as a guide to therapy. Thrombocytopenia may occur, especially after large doses. The leukocyte or platelet counts of an occasional patient may fall precipitously after even small doses of Cytoxan, as with all alkylating agents. The drug should be discontinued in such patients and reinstituted later at lower dosage after satisfactory hematologic recovery has occurred. Prior treatment with x-ray or with chemotherapeutic agents frequently causes an earlier or exaggerated leukopenia or thrombocytopenia after Cytoxan medication. Only rarely has there been a report of erythrocyte or hemoglobin reduction.
ADMINISTRATION: Add 5 cc. sterile water (Water for

Injection, U.S.P.) to 100 mg. of Cytoxan in the sterile vial (add 10 cc. to 200 mg. vial). Shake, allow to stand until clear, remove with sterile syringe and needle and inject.

The freshly prepared solution of Cytoxan may be administered intravenously, intramuscularly, intraperitone-ally, intrapleurally, or directly into the tumor. The solution should be administered promptly after being made but is satisfactory for use for three hours after preparation.

If the patient is receiving a parenteral infusion, the Cytoxan solution may be injected into the rubber tubing

if the solution is glucose or saline.

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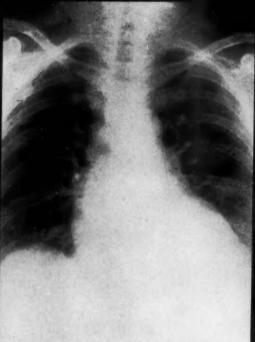
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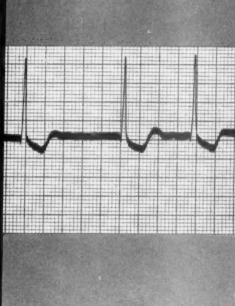
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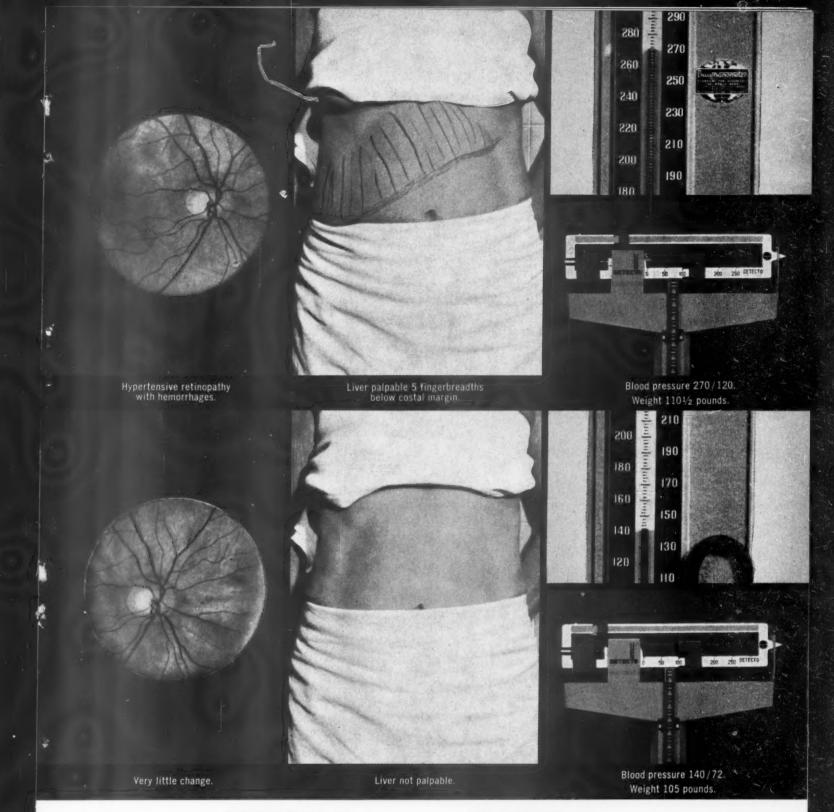
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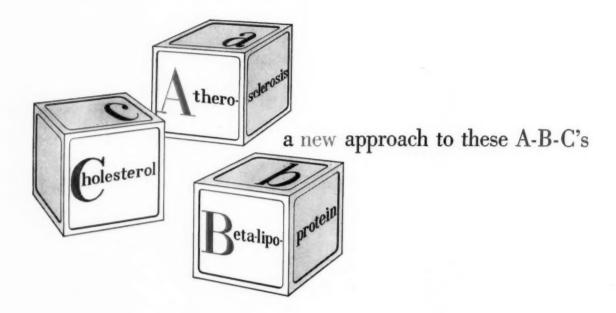
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1. Goldsmith, G. A.: Highlights on the Cholesterol-Fats, Diets and Atherosclerosis Problem, J.A.M.A. 176: 783-790 (June 3) 1961.

2. Olson, R. E.: Prevention and Control of Chronic Disease. I. Cardiovascular Disease-with Particular Attention to Atherosclerosis, Amer. J. Public Health 49: 1120-1128 (Sept.) 1959.

3. Wood, F. C., Gurin, S., and Kuo, P. T.: Medical Correlation Clinic on Atherosclerosis and Coronary Artery Disease, Am. Pract.-Dig. Treat. 12: 235-247 (April) 1961.

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1. Ford. R. V.: Current Therap, Res. 3:320, July, 1961.



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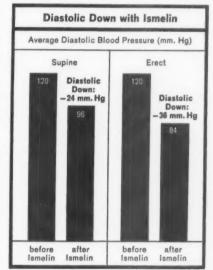
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References: 1. Brest, A. N. Novack, P., and References: 1. Brest, A. N. Novack, P., and Moyer, J. H.: To be published. 2. Harrison, T.R., Adams, R.D., Bennett, I.L.Jr., Resnick, W. H., Thorn, G. W., and Wintrobe, M. M. (Editors): Principles of Internal Medicine, The Blakiston Division, McGraw-Hill Book Company, Inc., New York, 1958, p. 1321.
3. Riven, S. S., and Hall, W.: South. M. J. 54:673 (June) 1961.

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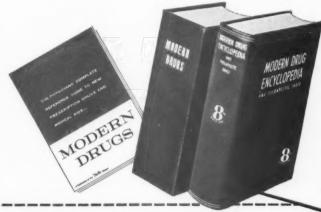
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San Francisco Blanchard-Nichols Associates YUkon 6-6341



Chicago R. H. Andrew, C. P. Haffner WAbash 2-7738

Los Angeles Blanchard-Nichols Associates TRemont 8-1935 Increasingly... the trend is to

Terramycine BRAND OF OXYTETRACYCLINE

confirmed dependability in fulminating infections is just one reason why



New evidence* demonstrates the effectiveness of Terramycin Intravenous in appendicitis with peritonitis... another reason for the trend to Terramycin.

In a 10-year study, Wenckert and Robertson (Malmo Hospital, Sweden) found that the mortality rate in appendicitis dropped dramatically from 1.17% to 0.22% after Terramycin intravenous therapy was used routinely in those cases with associated peritonitis.

Cases of appendicitis with peritonitis found during the course of 5,564 consecutive appendectomies were treated in the first 5 years with penicillin and/or streptomycin, and those in the latter 5 years with Terramycin administered intravenously and topically. Other procedures involved in the 2 five-year series, except the different antibiotic therapies used, remained essentially the same.

The authors report: "It would, of course, have been of value if the two groups compared had dated from the same period, but in view of the favourable impression soon made by Terramycin, it was not considered justified to deprive alternate patients of the benefit of the agent [Terramycin]."

These findings confirm the life-saving, broad-spectrum dependability of Terramycin Intravenous, as reported through more than a decade of extensive clinical use in serious or fulminating infections.

BRAND OF OXYTETRACYCLINE

vials containing 250 mg. and 500 mg., buffered with 1.0 Gm., 2.0 Gm. ascorbic acid, respectively

for most rapid and highest possible oxytetracycline blood levels / easily added to and compatible with most commonly used intravenous solutions / only 2 doses in 24 hours are necessary / well tolerated

Science for the world's well-being® (Pfizer)



PFIZER LABORATORIES Division, Chas. Pfizer & Co., Inc. New York 17, N. Y.

Wenckert, A., and Robertson, B.: Acta chir. scandinav. 120:79, 1960.



In brief

The dependability of Terramycin is based on its broad range of antimicrobial effectiveness, excellent toleration, and low order of toxicity. As with other broad-spectrum antibiotics, overgrowth of nonsusceptible organisms may develop. If this occurs, discontinue the medication and institute appropriate specific therapy as indicated by susceptibility testing. Glossitis and allergic reactions to Terramycin are rare. The usual precautions required in intravenous administration should be observed. See product brochure for full information. More detailed professional information available on request.

another reason why the trend is to Terramycin-versatility of dosage form:

TERRAMYCIN Capsules

250 mg. and 125 mg. per capsulefor convenient initial or maintenance therapy in adults and older children

TERRAMYCIN Syrup / Pediatric Drops

125 mg. per tsp. and 5 mg. per drop (100 mg/cc.), respectively-deliciously fruit-flavored, preconstituted aqueous suspensions

TERRAMYCIN Intramuscular Solution

50 mg./cc. in 10 cc. vials; 100 mg. and 250 mg. in 2 cc. ampules-preconstituted, ready to use where intramuscular therapy is indicated

PROTECTION IN ITS SIMPLEST FORM

IN ULCER THERAPY

ONE MEDICATION RELIEVES PAIN, INHIBITS EROSION, PROMOTES HEALING. UNIQUE IN SIMPLICITY. COMPLETENESS OF ACTION AND CONVENIENCE

Only ONE prescription to write



Marginal Esophageal

RESULTS

ACTIONS

RELIEVES SPASM AND REDUCES MOTILITY

RETARDS ACID PRODUCTION

PROMPT REDUCTION OF PAIN

RAPID AND PROLONGED NEUTRALIZATION OF GASTRIC HYDROCHLORIC ACID TO DESIRABLE pH LEVEL

 COATS AND PROTECTS **GASTRIC MUCOSA**

 INHIBITS EROSION OF **MUCOSA**

ANTICHOLINERGIC

orphenadrine hydrochloride ANTISPASMODIC

ANTISECRETORY

 TOPICAL ANESTHETIC orphenadrine hydrochloride

 ANTACID aluminum hydroxidemagnesium carbonate co-precipitate

 DEMULCENT bismuth aluminate

ANTIPEPTIC bismuth aluminate

INDICATIONS:
Peptic Ulcer:
Duodenal Marginal
Gastric Esophage
Hyperacidity and dyspepsia
Heartburn
Gastritis
Alcoholic gastritis
Castroserohageal reflux Alcoholic gastritis
Gastroesophageal reflux
Esophagitis (without stricture)
Irritable bowel syndrome
Congenital shortening of
esophagus
Chalasia of esophagus
Hiatus hernia of esophagus
Cardiosasem Cardiospasm Functional pylorospasm DOSAGE: Liquid and Tablets: 1 or 2 tablespoons or 1 or 2 tablets three times daily depending on severity of involvement. SIDE ACTIONS: Doses in excess of 6 tablets or 6 tablespoons daily may produce minor side actions such as dryness of the mouth or blurring of vision. or blurring of vision.

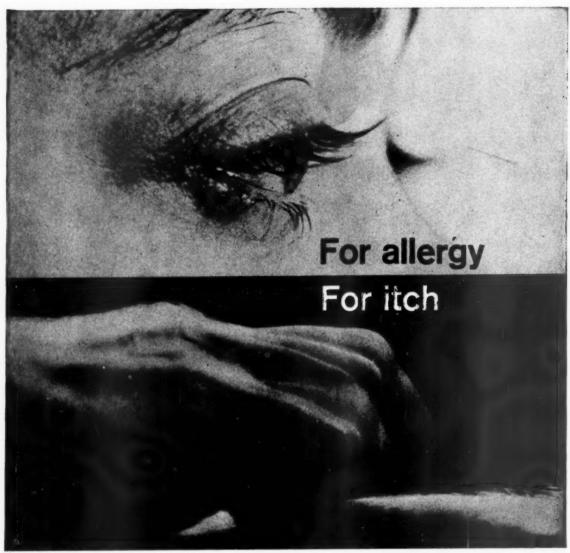
CONTRAINDICATIONS:
ESTOMUL should not be used in patients with organic pyloric obstruction or achalasia of esophagus. Use with caution in patients with renal impairment or insufficiency. Relative contraindications for anticholinergic drugs are glaucoma and prostatic hypertrophy which may lead to urinary bladder obstruction. AVAILABILITY: Tablets — Bottles of 100. Liquid — Bottle of 12 fluid oz.

CAUTION: Federal law prohibits

dispensing without prescription.

FORMULATION Each tablespoon (15 cc) ESTOMUL LIQUID contains: FORMULATION

Each ESTOMUL TABLET contains:
orphenadrine HCI
[2-dimethylaminoethyl (2-methylbenzhydryl) ether HCI]
bismuth aluminate. 25 mg. orphenadrine HCI
[2-dimethylaminoethyl (2-methyl-benzhydryl) ether. HCl]
bismuth aluminate. 50 mg. magnesium oxide aluminum 45 mg. hydroxide co-precipitate . . . 918 mg. co-precipitate . . . 500 mg. magnesium magnesium carbonate carbonate RIKER LABORATORIES, INC., Northridge, California



Everyday practice report:

Fellowing initial clinical investigational work, Forhistal was sent to physicians throughout the country for evaluation as an antiallergic and antipruritic agent in everyday practice. Results in 4026 cases have now been analyzed. In 2260 cases in which a comparison was made, Forhistal was judged better than previous therapy in 7 out of 10 patients. Information about the investigational work done previously is being mailed to you separately and is also available on request.

SUPPLIED: Tablets, 1 mg. (pale erange, scored). Lontabs, 2.5 mg. (orange). Syrup (pink), containing 1 mg. Forhistal maleate per 5-ml. teaspoon. Pediatric Drops (pink), centaining 0.5 mg. Forhistal maleate per 0.6 ml.

For complete information about Forhistal (including dosage, cautions, and side effects), see Physicians' Desk Reference or write CIBA, Summit, N.J.

FORHISTAL® maleate (dimethpyrindene maleate CIBA) LONTABS® (long-acting tablets CIBA)



Forhistal° rated better than previous therapy in 7 cases out of 10

Forhistal Lontabs® for greater convenience, smoother response, prelonged action.

2/ 29 LOHK-1